

THE JOURNAL OF PEDIATRICS

A MONTHLY JOURNAL DEVOTED TO THE PROBLEMS
AND DISEASES OF INFANCY AND CHILDHOOD

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'Procebrin' (Pan-Vitamins, Pediatric, Lilly) combines eight vitamins in a concentrated solution to help Johnny's bones grow straight, his body strong.

The fat-soluble vitamins A and D in 'Procebrin' are dispersed in a solution which assures absorption even when fat digestion is impaired. Uniform utilization, independent of the digestive process, adds greater efficiency to a plentiful formula.

Dropped on the tongue, the dose of 'Procebrin' has a pleasing taste. When diluted in milk or orange juice, it is quickly dispersed and is not easily detected.

Each 0.3 cc. of 'Procebrin' contains: Vitamin A, 3,000 units; Vitamin D, 800 units; Vitamin B₁, 1 mg.; Vitamin B₂, 0.5 mg.; Nicotinamide, 8 mg.; Pantothenic Acid (as Sodium Pantothenate), 1.5 mg.; Vitamin B₆ Hydrochloride, 0.5 mg.; and Ascorbic Acid, 60 mg.

prescribe

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in 15-cc. packages

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An Old Pewter Nursing Nipple



of Sainted Memory

but Not Sanitary

ATTRACTED by a reference to "The Mead Johnson Collection of Ancient Nursing Bottles," a medical friend sent in to us as a loan the interesting pewter nipple shown above. The nipple had been given to the physician by an elderly patient who had used it as a child in the 1840's. It had also been used by her mother, her grandmother, and other members of her family.

In the eighteenth century, feeding bottles too, were made of pewter, which is an alloy of about 80 per cent tin, with copper and lead or antimony. In the wealthier homes, feeding bottles and nipples were made of a special kind of pewter called Britannia metal, which contained tin, antimony and copper, and sometimes zinc. It was more easily fashioned on the lathe and could be nickel-plated or silver-plated. Those were

the days before bacteriology, and when one examines the long, narrow, inaccessible channel in this pewter nipple through which the infant sucked his feeding, and sees that the channel could not possibly be kept clean, one wonders that the infant mortality rate of those presanitation days was not even higher.

Nowadays, babies' bottles and nipples are easily cleansed and sterilized. Certified cow's milk contains a permitted maximum of only 10,000 bacteria per cubic centimeter. Dextro-Maltose,* the carbohydrate of choice of so many physicians, is practically sterile. Rigid control methods at the dairy and in the Mead Johnson Manufacturing Department, and care in the home combine to give modern babies sanitary protection not enjoyed by those babies that were fed through pewter nipples of sainted memory.

It is significant to reflect that it was through the efforts of physicians that safe, pure milk and sanitary dairy control came to be standardized and practised, and that Dextro-Maltose came into existence in response to the widespread demand of physicians for a carbohydrate that would give superior results in infant feeding.*

* U.S. Patent Office registered trademark of Mead Johnson & Company

MEAD JOHNSON & CO., EVANSVILLE, IND., U.S.A.

DAVOL NURSER with CONTROL VENT keeps time with BABY'S FEEDING!



Now feeding can be regulated according to baby's needs. The Davol Nurser (equipped with the famous "Anti Colic" Nipple) has a grand new feature—Control Vent. Just a simple turn of the regulator collar and the flow of the formula can be speeded up or slowed down in keeping with the baby's immediate requirements. The last ounce glides down as easily as the first. Easy feeding to the last drop.

The Davol Nurser is superior for a quartette of unbeatable reasons.

- The "Anti Colic" Nipple, constructed like the maternal nipple, encourages natural sucking
- The slimmer, streamlined bottle is easier to hold, quicker to clean
- The regulator collar controls the flow of formula and also holds the nipple firm
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through First Year' Mail the coupon, please

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DAVOL



Providence 2,
Rhode Island

*Reg U S Pat Of

Sick Children



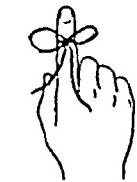
The rapidity with which eggless rennet-custards are digested—so easily made from uncooked milk with "Junket" Brand Rennet Powder or Tablets—especially recommends them in the infectious and febrile diseases which so often plague the young. When intestinal secretions are insufficient and digestive capacity and appetite impaired, light, easily digested and attractive foods are particularly welcomed. You will be pleased with the manner in which nutritious rennet-custards, quickly prepared in a wide range of colors and flavors, help to combat the "vicious circle" of flagging appetite and lowered resistance in the debilitated child.

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POWDER

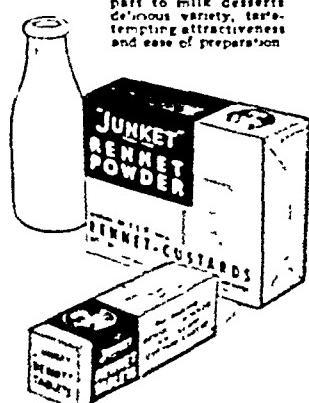
Chr. Hansen's Laboratory, Inc.
LITTLE FALLS, N. Y.

Make delicious rennet desserts with either
"Junket" Brand Rennet Powder, always sweetened, or popular flavor
"Junket" Brand Rennet Tablets (unsweetened and flavored
spoonsfuls of energy and digestibility)

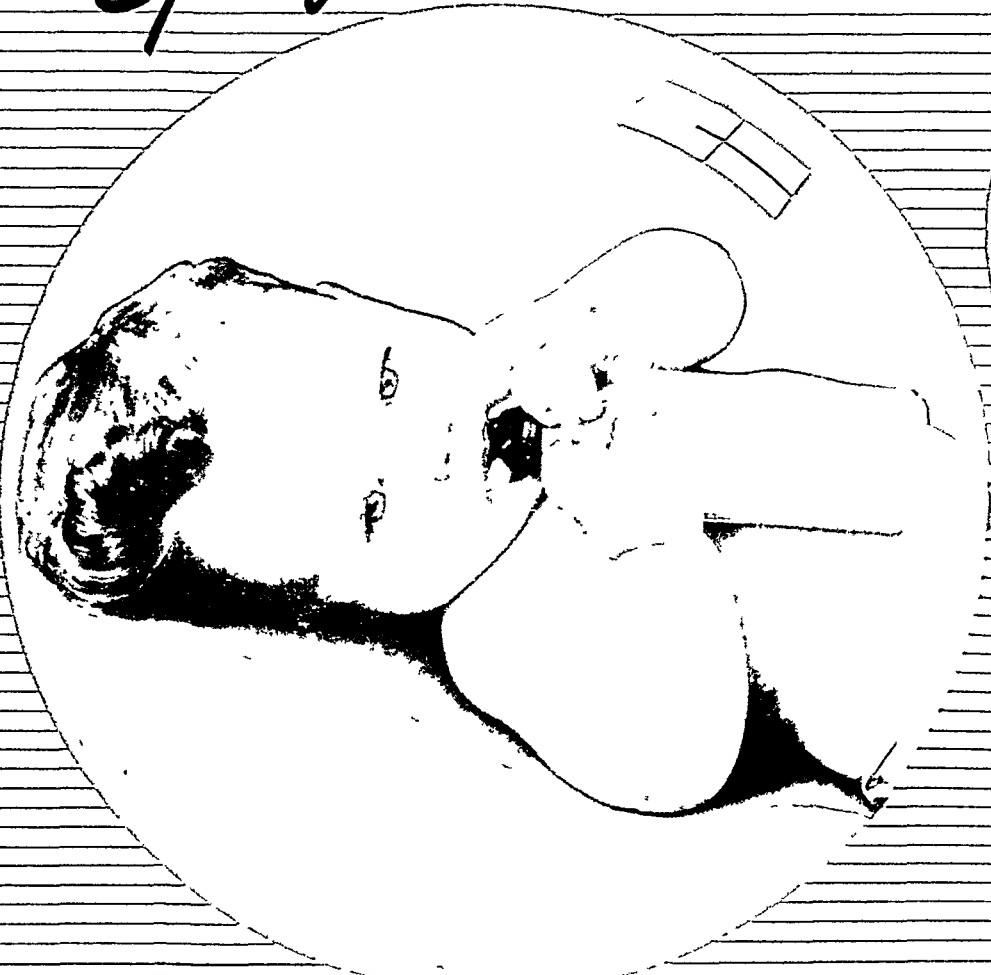
"JUNKET" is the trademark of Chr. Hansen's Lab., Inc.
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Just a reminder. Doctor Mothers will appreciate your inclusion of rennet desserts on your diet recommendations. They are part to milk desserts do'now variety, taste, tempting attractiveness and ease of preparation.



Specifically for babies



NEW DRISDOL®

**WITH VITAMIN A in (Sesame) Oil
NOW Also Milk Dispersible**

Contains 50,000 U. S. P. units of vitamin A (from fish liver oil) and 10,000 U. S. P. units of crystalline vitamin D₂ (calciferol) per gram, 1250 U. S. P. units of vitamin A and 250 U. S. P. units of vitamin D₂ per drop.

DOSE Same as Drisdol in Propylene Glycol

SUPPLIED in bottles of 10 cc and 50 cc

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*Less fermentation
in infant feeding*

CARTOSE

LIQUID

Cartose contains a mixture of carbohydrates:

dextrose, available for immediate absorption;

maltose, which is first split to dextrose;

dextrin, which is converted to maltose and then to dextrose.

The result is a steady supply of carbohydrate for "spaced" absorption and a low rate of fer-

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Cartose is produced under exacting conditions of cleanliness; the manufacturing process itself is sterilizing.

Compatible—easy to use; goes into solution almost instantly in milk or water—cold or warm—with no gummy particles. Stable and usable in all climates.

*To build sound
bones and teeth*

DRISDOL

Crystalline Vitamin D₃ (calciferol)

During the critical years when strong bones and teeth are being formed, Drisdol in Propylene Glycol affords an easy, economical way to assure an adequate intake of vitamin D. Disperses readily in milk and other liquids. Can be administered also in solid foods. Is odorless...tasteless...hyposalergenic. Average dose for

infants is only 2 drops in the daily ration of milk. For older children 4 to 6 drops and for pregnant and lactating women 5 to 10 drops daily are recommended.

Drisdol in Propylene Glycol is supplied in bottles of 5 cc., 10 cc. and 50 cc. with dropper delivering 250 U.S.P. vitamin D units per drop.

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When little patients

You provide sound therapy when you prescribe Sulfonamide *Dulcef* Tablets—and you obviate medicine-time tantrums. For *Dulcef* Tablets, with the full antibacterial power of equal weights of unflavored sulfonamides, have the good taste and appearance of candy mints. They neither look nor taste like medicine. Administering a *Dulcef* Tablet is only as difficult as giving a child a piece of candy.

An outstanding example of sulfonamides in this agreeable form is the DUOZINE *Dulcef* Tablet—a combination of sulfadiazine (0.15 Gm.) and sulfamer-

hit the ceiling

zine (0.15 Gm.). DUOZINE offers a new principle of safety in sulfonamide therapy: while its effectiveness is equal to 0.3 Gm. of either drug, the danger of crystalluria is no greater than if 0.15 Gm. of either drug were taken alone.

Try this effective method of administering sulfonamides on your next patient. DUOZINE *Dulcef* Tablets and the entire Sulfonamide *Dulcef* line listed below are available at prescription pharmacies everywhere. For descriptive literature on these tasty medicated sugar tablets, write to Abbott Laboratories, North Chicago, Ill.

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Abbott's Sulfadiazine-Sulfamerazine Combination

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(Sulfadiazine 0.15 Gm. and Sulfamerazine 0.15 Gm. Comb ned, Abbott)

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DUOZINE* *Dulcef* Tablets (Sulfadiazine 0.15 Gm. and Sulfamerazine 0.15 Gm. Combined, Abbott) • TRIAZOLINE® *Dulcef* Tablets (Compound Sulfadiazine 0.1 Gm., Sulfamerazine 0.1 Gm., and Sulfathiazole 0.1 Gm., Abbott) • DIAZOLINE® *Dulcef* Tablets (Compound Sulfadiazine 0.15 Gm., and Sulfathiazole 0.15 Gm., Abbott) • SULFADIAZINE* *Dulcef* Tablets, 0.15 Gm. and 0.3 Gm. • SULFAMERAZINE* *Dulcef* Tablets, 0.3 Gm. • SULFATHIAZOLE *Dulcef* Tablets, 0.3 Gm.

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FOR
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whenever
possible . . .
BREAST FEEDING
as long as
possible . . .

or

SIMILAC

*so similar to human breast
milk that there is no closer
equivalent*

1. THEREFORE, Less labor for baby—Easier to digest—zero curd tension.
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3. AND, Less labor for doctor—Easy to prescribe—1 measure Similac to 2 oz. water.

2 A HOLIDAY
FOR
MOTHER

SIMILAC DIVISION • N & R DIETETIC LABORATORIES, INC.



3 A HOLIDAY
FOR
DOCTOR

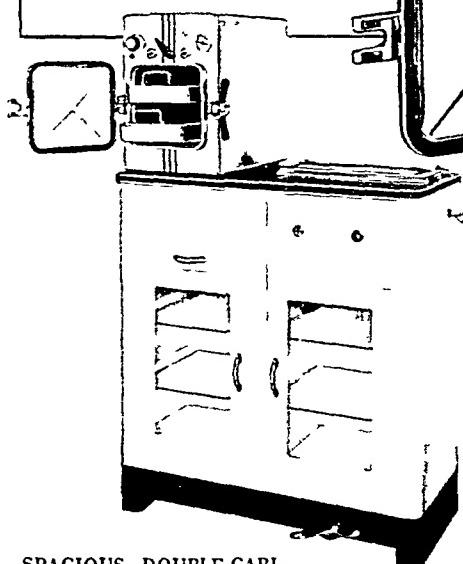
COLUMBUS 16, OHIO

Increases Load Capacity by 100%

Accommodates 2 instrument trays instead of one.

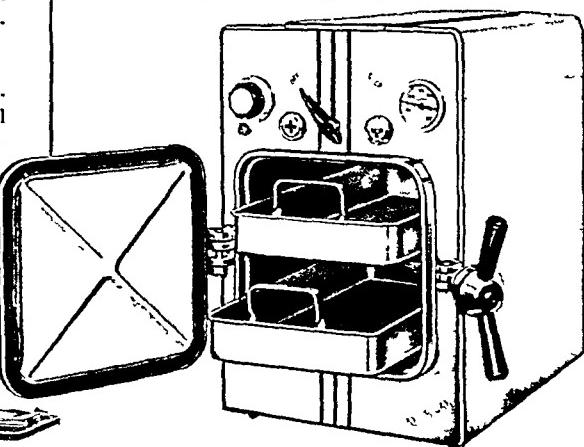
The "American" All-Purpose JUNIOR AUTOCLAVE (MODEL 8816)

- Fully automatic and self compensating for all types of load.
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Presents a radical departure in autoclave design that meets every requirement wherever a single, pressure steam sterilizer of small size is indicated. Duplicates in every respect the efficient, precision performance of standard size "American" Surgical Supply Sterilizers widely used in hospitals.



Diagrammatic comparison of Model 8816 and 8"x16" cylindrical type. Note accommodation of 2 instrument trays instead of one.

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Kanana Banana Flakes

Reg. U. S. Pat. Off.

not a powder

Sun-ripened bananas picked
and processed at their nutritional peak

Useful in the control of diarrheas of infancy and celiac disease. For high calory and hypo-allergenic diets, Kanana Banana Flakes provide an important food that is uniform and ready for instant use.

Kanana Banana Flakes are made from the Canary variety of banana which is the reason why they have a high vitamin C content (36 mg per 100 gm) and a sugar content of 83%.



The 5½ oz. can contains
20 six inch size bananas.

THEY COST LESS THAN RAW FRUIT



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September, 1942

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DAPTA
means
full
vitamin
potencies
Wyeth

Dapta is stable, as confirmed by repeated assays. Therefore, you can be certain of the full vitamin intake prescribed when you specify Dapta for infants and children.

Dapta is nonoily, assuring efficient utilization. It is pleasant-tasting, readily miscible with milk and other foods.

Recommended dosage: Infants, 0.5 cc. daily; children 1 to 6, 1 cc. daily.



WYETH INCORPORATED • PHILADELPHIA 3, PA.

Two Hour Blood Levels¹
Additive Therapeutic Effect²
Less Toxic³

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MICRO
CRYSTALLINE

SULFA

MERAZINE

SULFONSOL —A DELICIOUS LIQUID SUSPENSION OF MICRO CRYSTALLINE SULFADIAZINE AND SULFAMERAZINE—is far superior to bulky tablet medication. Each 8 cc. (2 teaspoonsfuls) is therapeutically equivalent to the standard half-gram (0.5 Gm.) sulfonamide tablet. Since each drug is present in micro crystalline form a desired total sulfonamide blood level is attained in 2 hours instead of the usual 6 hours.

The therapeutic effects of sulfadiazine and sulfamerazine are additive—yet these two drugs are independently soluble in body fluids. Hence, their simultaneous administration, on the basis of total sulfonamide content, constitutes the logical answer to the problem of crystalluria which frequently follows the administration of full doses of either drug alone. Furthermore, the serious toxic reactions occasionally associated with sulfathiazole, such as hematuria, are seldom encountered following the use of sulfadiazine or sulfamerazine.

Supplied in bottles of 2, 4 and 16 fluidounces.

1. Reinhold, J. G., Phillips, F. J. & Flippin, H. F.: Am. J. Med. Sci., 210:141, 1945.
2. Leibr, D., Slobody, L. B., & Greenberg, W. B.: J. Pediat., 29:275, 1946.
3. Leibr, D.: Proc. Soc. Exper. Biol. & Med., 64:393, 1947.

SULFONSOL

micro crystalline sulfadiazine-merazine

THE NATIONAL DRUG COMPANY, PHILADELPHIA 44, PA.

Manufacturers of



Pharmaceutical,
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Biochemical Products
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now:

the 2 safest sulfonamides combined in palatable fluid form

"The value of sulfonamide mixtures in reducing crystalluria and renal complications is based on undisputed experimental evidence."¹

ESKADIAMER is a combination of the two safest sulfonamides now in general use—sulfamerazine and sulfadiazine.



Children—and adults who balk at bulky half-gram tablets—take ESKADIAMER willingly because it tastes good and is easy to swallow. Because ESKADIAMER is so unusually palatable, it is particularly useful when a prolonged course of therapy (as in prophylaxis) is indicated.

1. Lehr, D.: Sulfonamide Mixtures, J.A.M.A. 139:398 (Feb. 5) 1949

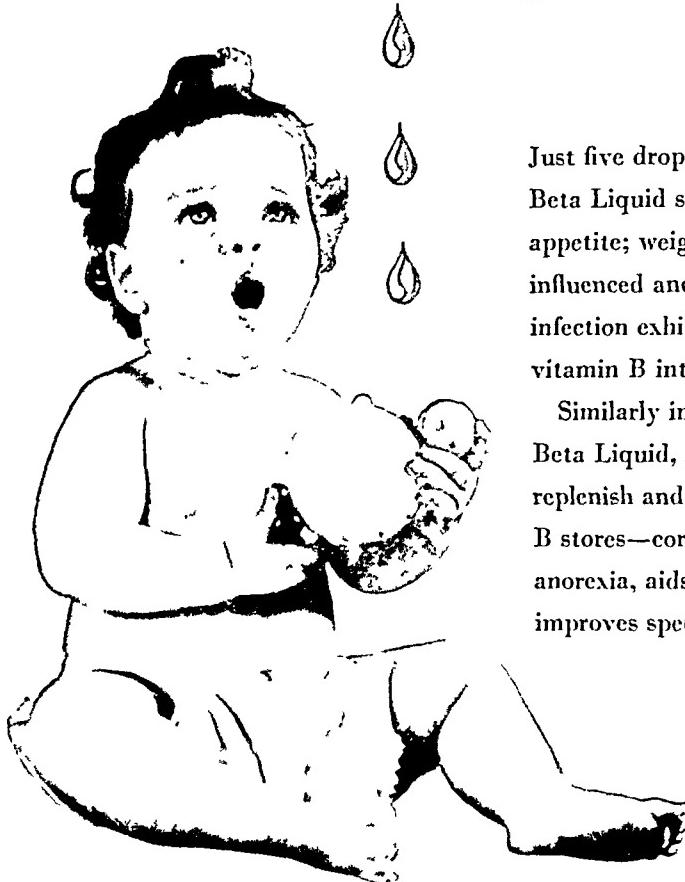
Eskadiamer

the delicious fluid preparation of sulfamerazine and sulfadiazine

Smith, Kline & French Laboratories, Philadelphia

Each 5 cc. (one teaspoonful) contains 0.25 Gm. (3.86 gr.) microcrystalline sulfamerazine and 0.25 Gm. (3.86 gr.) microcrystalline sulfadiazine—the dosage equivalent of the standard 0.5 Gm. (7.7 gr.) sulfonamide tablet.

infant anorexia rapidly disappears



Just five drops daily of White's Multi-Beta Liquid stimulates the infant appetite; weight increase is favorably influenced and greater resistance to infection exhibited—the early infant's vitamin B intake is at a safe range.

Similarly in the adult, White's Multi-Beta Liquid, in teaspoon dosage, helps replenish and maintain adequate vitamin B stores—corrects deficiency-induced anorexia, aids in patient recovery, improves special or restricted dietaries.

EXCELLENT PRESCRIPTION INGREDIENT

Palatable, non-alcoholic and stable, White's Multi-Beta Liquid is ideally suited to pre-scription use. Compatible with such ingredients as: (1) Tincture Nux Vomica, in equal parts, (2) Elixir Phenobarbital, 1 to 4 parts, (3) White's Mol-Iron Liquid, 1 to 8 parts.

White's



ULTI-BETA LIQUID

... multi-purpose B complex source

WHITE LABORATORIES, INC., Pharmaceutical Manufacturers, NEWARK 7, N. J.
September, 1949

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***Citrus fruits**—among the richest known sources of vitamin C—also contain vitamins A, B₁ and P, readily assimilable natural fruit sugars, and other factors such as iron, calcium citrates and citric acid.

-building . . .

with the aid of citrus fruits and juices!

Natural vitamin C—ingested in ample quantities daily—constitutes a significant contributory factor in the achievement of optimal nutrition³ in infants and children. Among food sources of this essential vitamin, citrus fruits are almost unique in the remarkable richness of their ascorbic acid, plus natural fruit sugars¹ and other important nutrients.*

Collagen formation (and concomitant tissue integrity),³ mineral metabolism and calcium utilization are all beneficially influenced by a daily dietary adequacy of vitamin C, with consequent improvement in stamina, bodily vigor, and resistance to disease.²

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FLORIDA CITRUS COMMISSION • LAKELAND, FLORIDA

references: 1. McLester, J. S.: Nutrition and Diet, Saunders, 4th ed., 1944.
2. Rose, M. S.: Rose's Foundation of Nutrition, rev. by MacLeod & Taylor, Macmillan, 4th ed., 1941. 3. Sherman, H. C.: Chemistry of Food and Nutrition, Macmillan, 7th ed., 1946.



FLORIDA

Oranges • Grapefruit • Tangerines

Delayed release...



Just as a great dam stores and releases water only as fast as the fertile lands below can utilize it, so does Alhydrox* adsorb antigens and release them slowly from tissue after injection. This gives the effect of continuous small doses.

Alhydrox is a Cutter exclusive—developed and used by Cutter for its vaccines and toxoids. It supplements the physician's skill by producing these immunizing advantages:

1. *Alhydrox selectivity controls the absorption of antigens, reducing dosage volume while building a high antibody concentration.*
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* Trade name for Aluminum Hydroxide Adsorbed

Specify these Cutter Alhydrox Vaccines

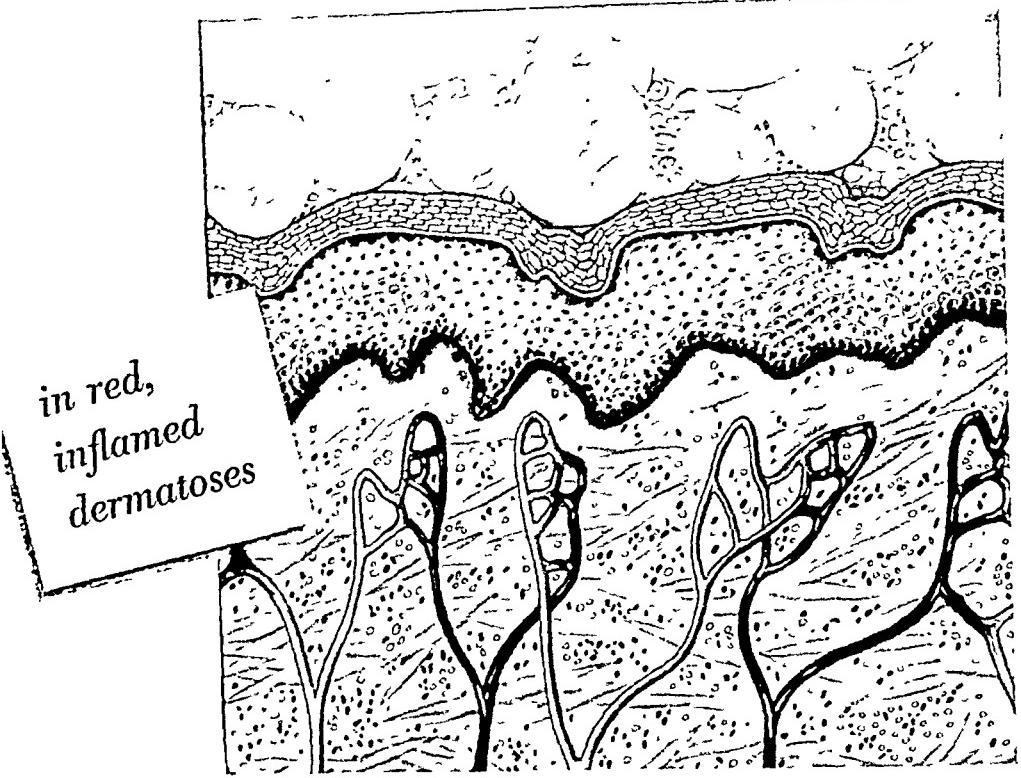
- Pertussis Phase I Alhydrox
30 000 million H pertussis per cc
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- Diphtheria Toxoid Alhydrox
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Cutter Diphtheria Toxoid plus 20 000 mill. H pertussis per cc for simultaneous immunization against pertussis and diphtheria
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For simultaneous immunization against diphtheria and tetanus
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Cutter diphtheria pertussis tetanus combined vaccine for simultaneous immunization against diphtheria pertussis tetanus

**Trade Mark

Your Cutter dealer has Alhydrox vaccines in stock

Alhydrox is exclusive with

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first avoid irritation

Unwitting use of ordinary soap may irritate already inflamed skin. Prohibition of soap as a first step in dermatologic therapy will protect against the possible harmful effects of alkalis, fatty acids and the keratolytic and allergenic properties which often nullify therapeutic efforts.

with *pHisoderm*®

To enable the patient to cleanse the skin more effectively and safely without irritation, prescribe pHisoderm, a non alkalizing, soapless, sudsing detergent, active in water of any degree of hardness. pHisoderm, with a pH value of 5.5 equal to that of normal skin, leaves intact the skin's protective "acid mantle." It reduces surface tension for thorough cleansing. It is an invaluable adjunct in the therapy of all dermatoses when proper cleansing is essential.

pHisoderm—composed of ether sulfonate, lanolin cholesterol, petrolatum and water. Supplied in Regular, Oily and Dry Types, bottles of 2 oz., 7 oz., 12 oz. and 1 U.S. fl. oz.; 1 m. l. oz. refillable hand dispensers.

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The Place

Prominent Hospitals

The Tests

Jergens Lotion against Usual
Hospital Skin Cares



The Results

Jergens Lotion Proved Indicated
Care for Baby Skin

Here are facts regarding baby skin care that should be of unusual interest to the profession:

An intensive series of tests has recently been completed in leading hospitals, under the guidance of staff pediatricians.

Jergens Lotion and three treatments commonly used in hospitals were tested on the skins of hundreds of newborn infants. The four treatments tested were:

1. Mineral Oil
2. Soap and Water
3. Cornstarch and Soap and Water
4. Jergens Lotion

The skins were observed for a period of two weeks for incidence of rashes: macules, papules, and pustules.

The results indicated that Jergens Lotion gave 5 times better protection against the skin irritations mentioned than the three other listed treatments.

You can recommend Jergens Lotion to your patients as a superior daily skin care for newborn infants.



Jergens Lotion is sterile, does not support bacterial growth. Active ingredients: Glycerine, Sweet Almond Oil, Spermaceti, Benzaldehyde, Gum Benzoin, Alcohol.

If you have not already received your copy of these Hospital tests, write to the address below and the report will be mailed to you promptly.
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SALICYLAMIDE COMPOUND
(DONLEY-EVANS)

DECOSAL provides the most potent salicylate compound, Salicylamide . . . as harmless as aspirin, yet has 2.08 times the analgesic potency of sodium salicylate and 7.5 times the analgesic potency of aspirin.

in an uncoated, crush-up tablet
or palatable liquid

RELIEF
without
REACTION

in rheumatic fever and arthritis

DECOSAL obviates untoward hematic effects (hypoprothrombinemia) or depression of vitamin C levels encountered with large doses of salicylates.

DECOSAL is singularly free from unpleasant gastro-intestinal side-effects common to the use of salicylates.

DECOSAL, containing Salicylamide, Succinic Acid and Ascorbic Acid, provides a unique salicylamide compound for prolonged and intensive therapy. Salicylamide is the drug of choice for unexcelled analgesic potency; succinic acid confers positive protection against salicylate toxicity. DECOSAL, a notable achievement in salicylate therapy, thus affords a new approach to the routine treatment of rheumatic fever

and arthritis in providing prompt action and optimum absorption without unpleasant toxic or pro-thrombinopenic effects.

Literature and sample on request.

DONLEY-EVANS & COMPANY



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Robins

[] broadens the scope of

Effective Anti-Arthritic Therapy

with

Pabalate® Liquid

From laboratory dream to clinical reality—that's the story of Robins' new anti-rheumatic Pabalate, the unique combination of para-aminobenzoic acid and sodium salicylate which provides higher salicylate blood levels on lower salicylate dosage. Now, further implementing the clinical value of this important new formula, Robins offers another outstanding research development: easily-administered, pleasant-tasting Pabalate Liquid! With Pabalate Tablets and Liquid, the physician can now more effectively treat patients with rheumatic fever or other rheumatic disease, at all age levels—from infancy to old age!

FORMULA: Sodium salicylate and Para-aminobenzoic acid (as sodium salt) of each, (5 gr.) 0.3 Gm. in each 5 cc. (1 teaspoonful) of a chocolate flavored liquid, or an enteric coated tablet.

INDICATIONS: Rheumatoid arthritis; acute rheumatic fever; fibrositis; gout; osteo-arthritis.

DOSAGE: Average adult dose: two teaspoonfuls or two tablets, three times daily.
Dosage for children proportional to age and severity of condition.

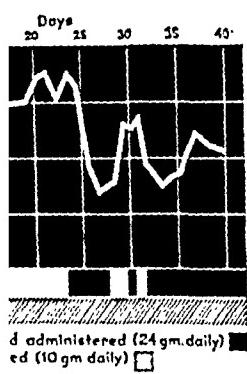
A. H. ROBINS CO., INC. RICHMOND 20, VIRGINIA
Ethical Pharmaceuticals of Merit since 1878

*For higher salicylate blood levels
on lower salicylate dosage—*



Pabalate
TABLETS AND LIQUID





d administered (24 gm. daily) ed (10 gm daily)



NEOHETRAMINE® Hydrochloride

**Safe
Dependable
Relief
in
Hay Fever**

Clinical experience shows . . . "In seasonal hay fever it was noted that only 18% had no relief and in perennial allergic rhinitis only 20% had no relief, when using Neohtetramine."

Aaron, T. H. & Cripe, L. H.: Canad. M.A.J. 59:438, Nov. 1948

"Its very low incidence of side actions makes it frequently a drug of choice."

Bernstein, T. B. & Feinberg, S. M.: J. Allergy 19:393, Nov. 1948

Prescribe NEOHETRAMINE hydrochloride as your first choice in antihistaminic therapy. Less toxic in effective doses.

Tablets—25 mg., 50 mg., 100 mg.; Syrup—6.25 mg. per cc.; bottles of 1 pint and 1 gallon; Cream—2%, tubes of 1 ounce.



WYETH is a registered trademark of the Nepera Chemical Company, Inc. Neohtetramine hydrochloride is dimethyl-N'-p-methoxyne monohydrochloride.

WYETH INCORPORATED • Philadelphia 3, Pa.

Summer Comfort...

JUMPING-JACK protection

Little feet are cool, free, yet well protected in Jumping-Jack summer shoes.
Heels snugly cradled, foot kept well centered, yet Jumping-Jack flexibility permits complete foot freedom.



JUMPING-JACKS
FLEXIBLE SHOES FOR HARD WEAR

FOR ALL CHILDREN 6 MONTHS TO 4 YEARS

VAISSEY-BRISTOL SHOE COMPANY, INC.
ROCHESTER, NEW YORK
MANUFACTURED IN HEGAN, MAINE

A GREAT PAIR

of **SOAPLESS**
DETERGENTS

LOWILA

CAKE * LIQUID

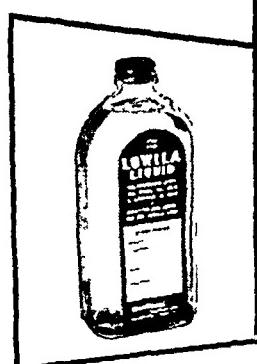
**When soap is taboo in DIAPER
RASH and INFANTILE ECZEMAS**

LOWILA CAKE for skin cleansing

The only detergent cake which is entirely soapless yet cleanses as well as soap. No alkali whatsoever, pH approximates normal skin, never irritates. Less slippery than ordinary soap so mother can hold baby more firmly while bathing. Good lather.

LOWILA LIQUID for clothes
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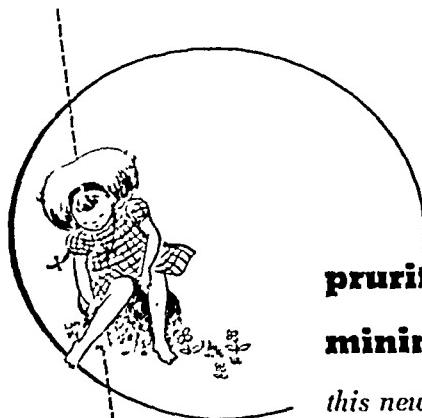
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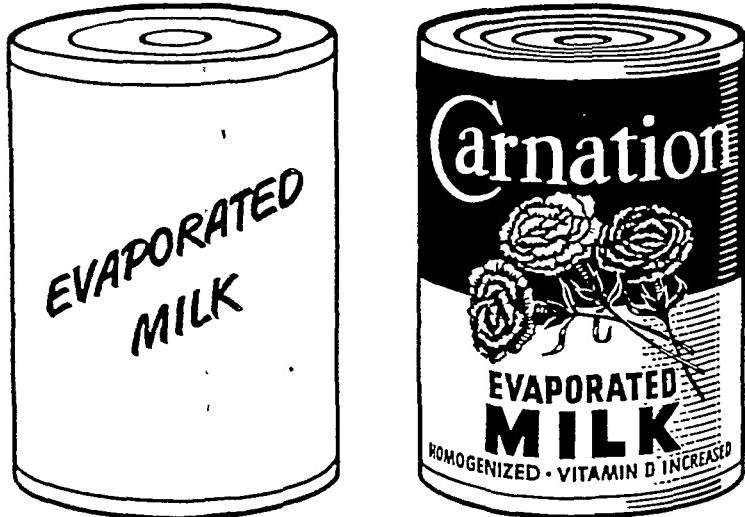
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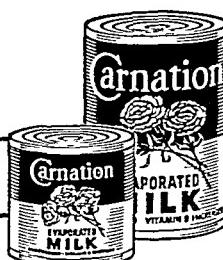
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- 1 Gaul, L E JAMA 127 439 1945
- 2 Underwood G B and Gaul L E JAMA 139 570 1948
- 3 Underwood G B, Gaul, L E Collins E and Nestor, M JAMA 130 247, 1946
- 4 Andrews, G C Diseases of the Skin Philadelphia W B Saunders Co 1946
- 5 Ornitby, O S Diseases of the Skin Philadelphia, Lea and Febiger, 1937
- 6 Gaul, L E Hygeia 23 250, 1945

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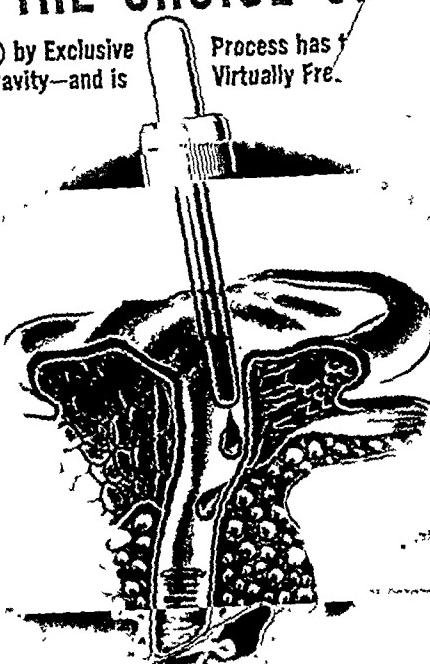
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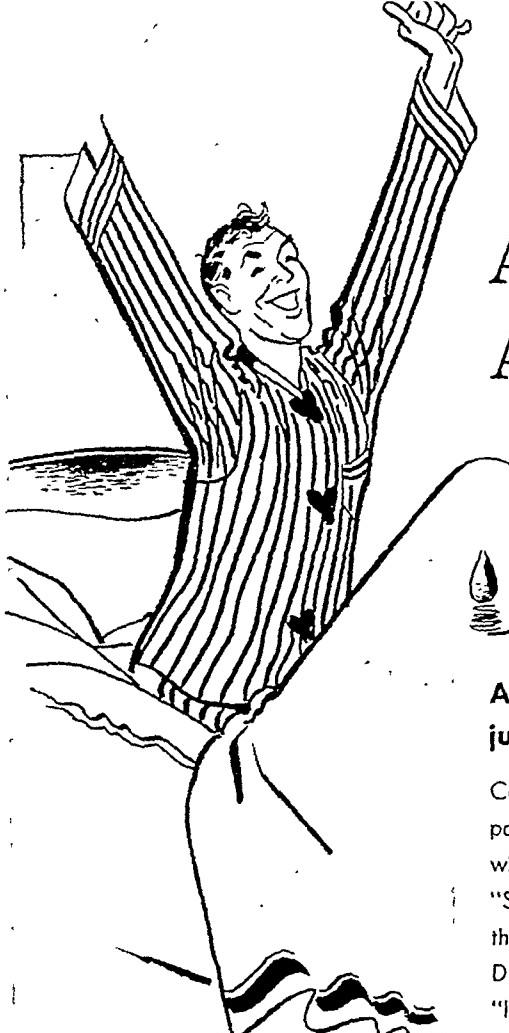
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1. Sheldon, J. M. et al: Univ. Mich. Hosp. Bull. 14:13-15 (1948). 2. MacQuiddy, E. L.: Neb. State M. J. 34:123 (1949)



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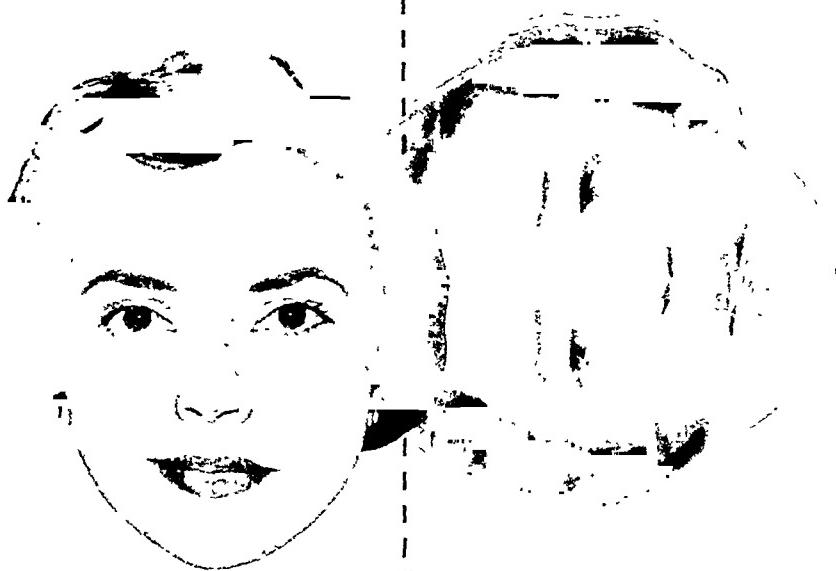
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I-Hansel, F. K. • Ann. Allergy, 5:397, 1947.

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Adequate Breakfast Habits AND MENTAL ACUITY

Recent physiologic research* conducted at the Departments of Physiology and Nutrition of an outstanding medical college has demonstrated a positive correlation between breakfast adequacy and mental acuity at the pre-noon hour. By inducing greater physiologic efficiency, breakfast routines providing 800 or 400 calories reduce the simple and choice reaction times to external stimuli whereas the habits of omitting breakfast or the taking of coffee only produce the opposite effect.

The effects of the four different breakfast practices were studied under strictly controlled conditions using six young women graduate students as subjects. Since reaction time is particularly sensitive to alterations in physiologic conditions, this test was adopted for detecting changes in the mental acuity states of the experimental subjects. The findings of the 800 calorie breakfast period were adopted as the standard base of reference.

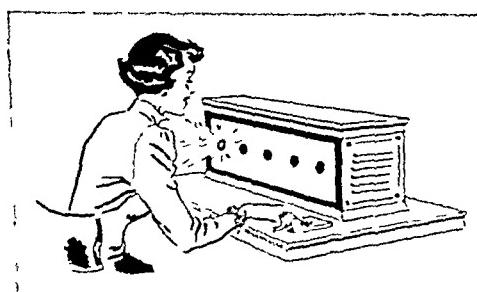
Conclusions drawn from this important work are:

1. When no breakfast was the morning practice, a notable *increase* resulted in the duration of the simple and choice reaction times.
2. Habituation to coffee only induced a similar *increase* in reaction time.

3. When habituation to the 400 calorie breakfast was attained after the coffee only period, both simple and choice reaction times showed a noteworthy *decrease*.

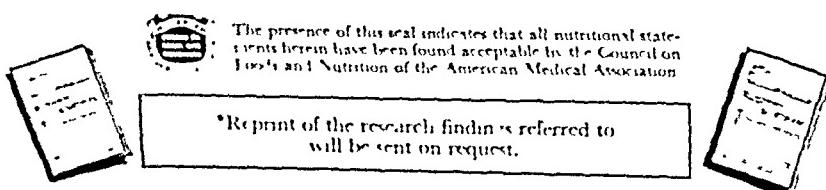
This physiologic research, for the first time, presents directly derived experimental evidence supporting the recommendation long propounded by nutrition and health authorities for eating an adequate breakfast. For planning such nutritionally acceptable breakfasts the widely acclaimed basic breakfast pattern of fruit, cereal, milk, bread and butter serves as an excellent nutrient foundation.

Although not stated in the published report, the findings forcefully intimate that during the late morning greater mental acuity results from adequate breakfast practices than when omission of breakfast or coffee only is the morning habit.



 The presence of this seal indicates that all nutritional statements herein have been found acceptable by the Council on Foods and Nutrition of the American Medical Association

*Reprint of the research findings referred to will be sent on request.

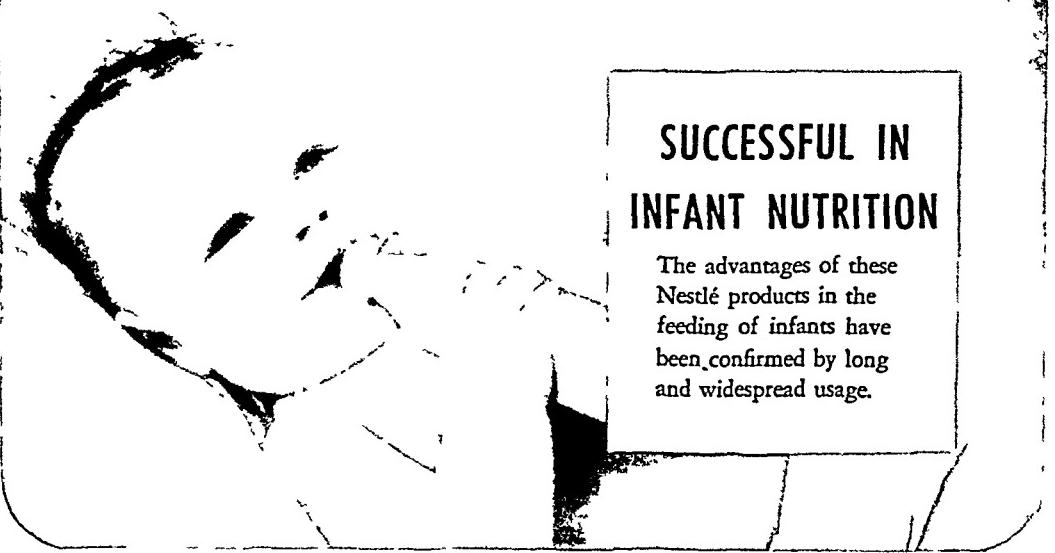


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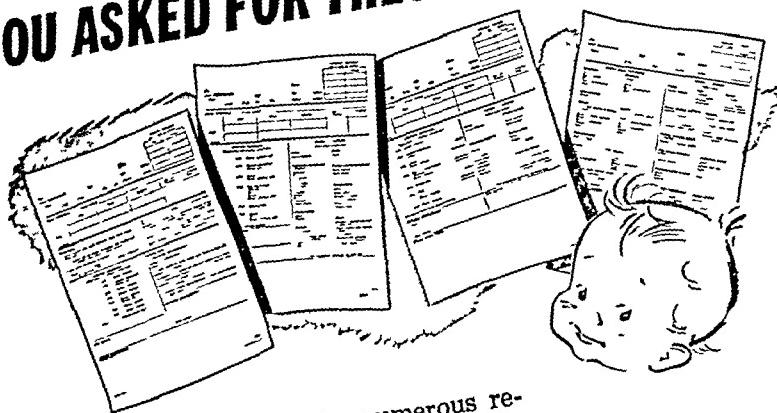
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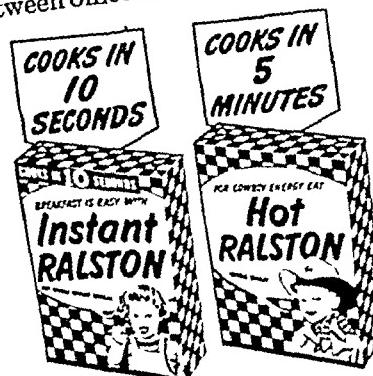


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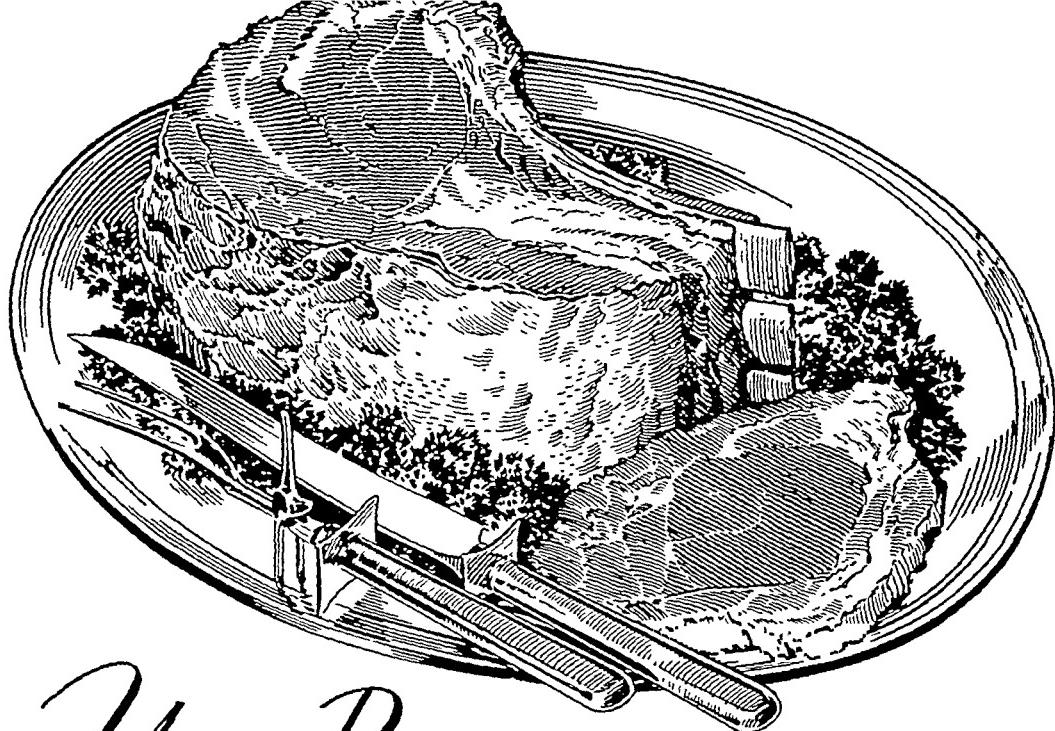
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*McLester, J S : Protein Comes Into Its Own, J.A.M.A. 139:897 (April 2) 1949.



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Declid Undecylenic Acid Capsules are to be dispensed only by or on the prescription of a physician. Supplied in Bottles of 100 or 1,000 Capsules, 0.41 gram each. Complete literature on request.

REFERENCES

1. Perlman, H. H.: Undecylenic Acid Given Orally in Psoriasis and Neurodermatitis, J.A.M.A. 139:444 (Feb. 12) 1949.
2. Perlman, H. H., and Milberg, I. L.: Peroral Administration of Undecylenic Acid in Psoriasis, J.A.M.A. 140:865 (July 9) 1949.

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* Vital Statistics—Special Reports, Vol. 25, No. 12, National Office of
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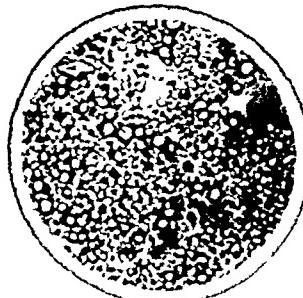
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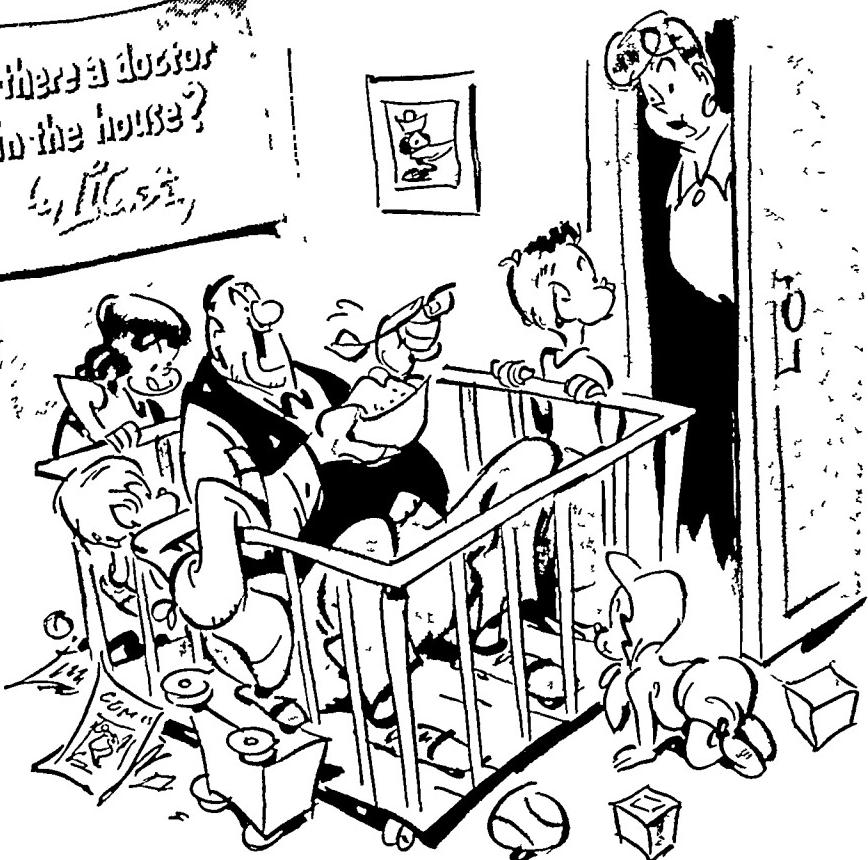
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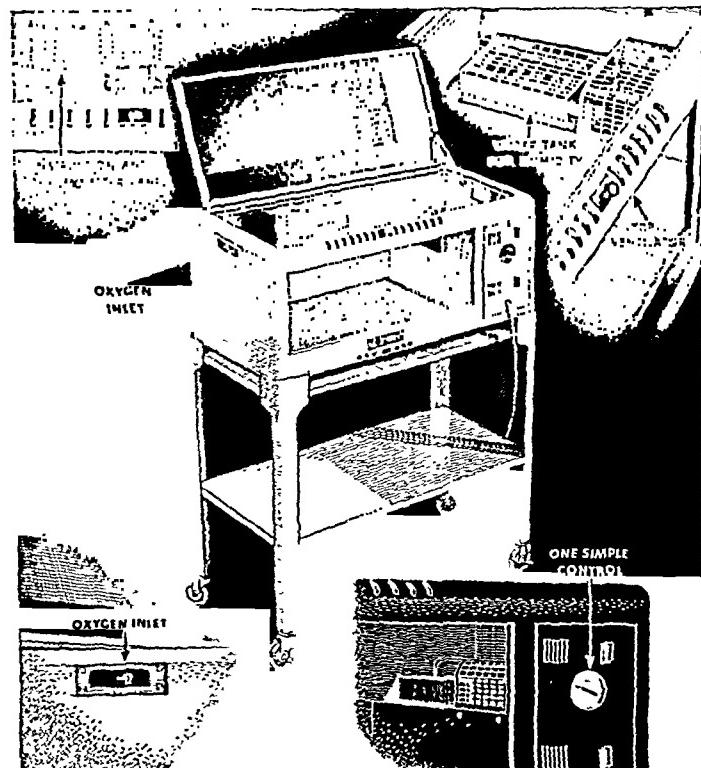
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Original Communications

THE EFFECT OF SPECIFIC THERAPY ON THE COMMON CONTAGIOUS DISEASES

PRESIDENTIAL ADDRESS

JEAN V. COOKE, M.D.
St. Louis, Mo.

THE subject on which I have chosen to speak to you today, The Effect of Specific Therapy on the Common Contagious Diseases, is one which could be studied by several methods. The usual one is by observing a selected group of patients and noting the effect of certain specific therapeutic measures as compared with a similar control group or with previous experience with similar untreated patients. All of us have used this method and have observed that specific therapy has a striking effect on certain of these diseases. The wide application of such therapy and its influence on the general population is of considerable importance since, when truly effective, the results of specific therapy should be widespread and reflected nationally on the mortality of a disease or on its incidence or on both. Accordingly, the method selected was to examine the mortality statistics for certain of the common contagious diseases in recent years and to observe the possible effect on them that might be attributed to specific therapy.

The data analyzed were from the annual reports of the vital statistics of the United States Bureau of the Census in recent years through 1945, which was the last report available. In mortality statistics it is traditional to speak of the mortality rate or deaths per 100,000 of the population of all ages. Since, in the contagious diseases to be considered, a very high percentage of deaths occurs during childhood, the mortality rate for children alone will be shown in certain instances. This is, of course, considerably higher than the general mortality rate but would seem to give a somewhat more accurate picture of the menace of the diseases in children. For such childhood rates, the figures from the 1930 census were used for the years 1926 through 1935, and those from the 1940 census for the years 1936 through 1945, which seemed sufficiently accurate for this purpose. In this connection it is of interest that although the population of the continental United States increased from

122,775,000 in 1930 to 131,954,000 in 1940, or approximately 9,000,000, the census figures for children under 15 years of age decreased from 36,057,000 in 1930 to 32,972,000 in 1940, or about 3,000,000, which is a fall from 29.4 per cent of the total population to 25 per cent.

In conjunction with the mortality figures, the morbidity in the United States for various years was also tabulated from the Bulletins of the U. S. Public Health Service. It must be understood that such morbidity figures are somewhat incomplete since many cases are unreported. However, since they are reported under comparable conditions from year to year, they are valuable in showing the relative annual prevalence of the diseases and especially those years in which the diseases are epidemic, because mortality has a natural relationship to the incidence. Before presenting any of the data, I should like to anticipate by stating that a most striking decrease in the mortality of several of the common contagious diseases has occurred in the past decade. The relation of this fall in mortality to the introduction of the sulfonamide drugs is so close as to leave little doubt that this form of specific therapy has had a greater effect upon the mortality of most of the common contagious diseases than is generally appreciated. Sulfanilamide came into general use in 1937, followed by sulfapyridine in 1939, sulfathiazole in 1940, and sulfadiazine in 1941, and all have been widely and increasingly employed during the succeeding years. All have been quite effective in pyogenic infections, although the more recent ones have certain advantages. Penicillin was not generally available until 1945, so that it cannot be considered in the data to be presented.

A general picture of the mortality of infectious disease in recent years is illustrated by the figures of all infectious and parasitic diseases, one of the categories summarized in the vital statistics data. This is seen in Graph 1, in which the total deaths and the mortality rate are shown. It will be noted that deaths ranged from 150,000 to 160,000 from 1930 to 1937, and that a sharp drop occurred in 1938 to around 120,000 with a still further fall to around 100,000 in 1942. As is to be expected, the general mortality rate follows closely the curve of deaths and shows a similar fall. It is of interest that this decrease is sustained and progressive and that although many factors are concerned in mortality statistics, any abrupt and prolonged change must be due to some new and potent element.

Not included in these figures on all infectious and parasitic diseases are those of the deaths due to pneumonia, which are shown in Graph 2. Here are illustrated the annual deaths from all forms of pneumonia, including lobar and bronchopneumonia and capillary bronchitis. Although there is a peak in the curve in 1936 with definite increased incidence in 1935 and 1937, the definite fall in mortality after this is evident, so that the levels in the later years of the graph are only somewhat more than one-half as high as in earlier years. This considerable increase in pneumonia deaths in 1936 was apparently in adults since, as will be seen later, it did not occur in children. Pneumonia has a special significance in the mortality of certain of the common contagious diseases, notably whooping cough and measles, so that particular attention was

paid to the pneumonia mortality in children, as shown in Graph 3. Here are noted the death rates in children under one year, from one through 4 years, and from one through 14 years. In all groups it will be seen that there is little variation in the mortality rate in the years preceding 1938, but in that year and succeeding years there is an evident decrease in the 1- to 4-year and 1- to 14-year groups, so that in both of these the rate fell rather rapidly to a point little more than one-half of its previous levels. The death rate in children under one year, however (the heavy line), which was somewhat more than 800 per 100,000 prior to 1938, showed a decrease later to only around 700 per 100,000, or very much less striking than in children over this age, since the fall in the 1- to 4-year group (the lighter solid line) was from over 80 to around 50, and of all those children over one year (the lower broken line) from over 30 to less than 15. This difference in the mortality rate in infants under one year as compared with older children is emphasized again in Graph 4, in which the mortality rate in this infant group is shown with its percentage to all pneumonia deaths in children. Although the moderate fall in deaths after 1938 is still apparent, it will be seen that, of all the deaths from pneumonia in children, those in infants under one year increased from a percentage of 65 or below before 1938 until a few years later it had reached 75 per cent of all pneumonia deaths in children. This emphasizes the fact that the factors associated with the decreased mortality in older children were much less effective in infants under one year. This same discrepancy will be noted later in connection with the deaths from whooping cough and measles, in both of which diseases pneumonia plays a most important role in mortality, and a possible explanation will be suggested.

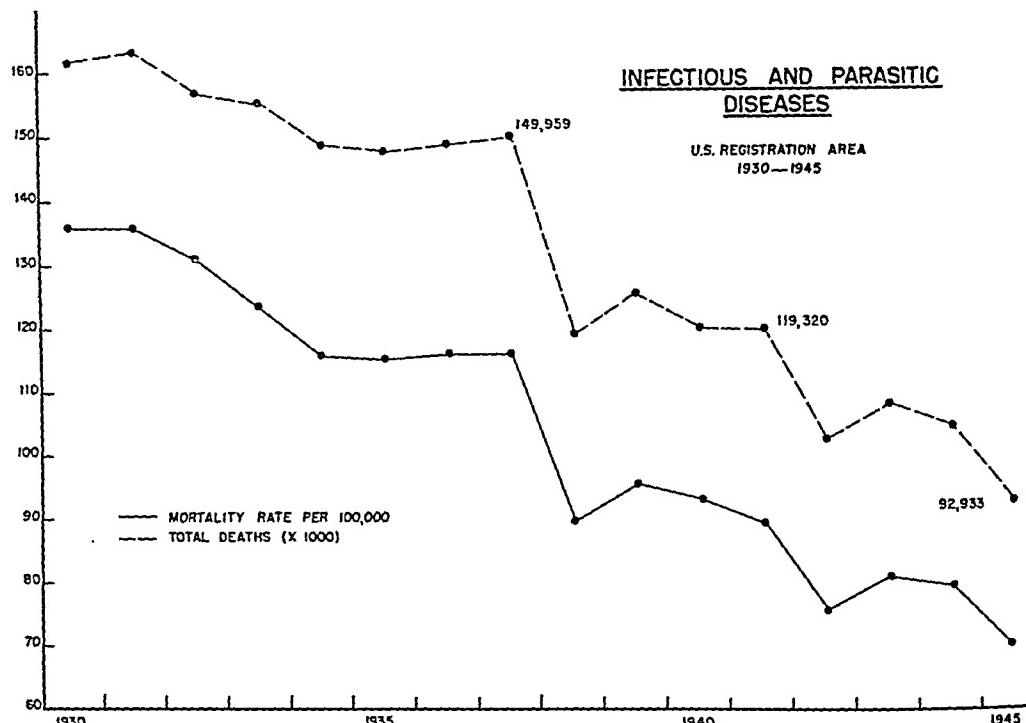
In reviewing separately the common contagious diseases, I shall include only diphtheria, scarlet fever and erysipelas, measles, whooping cough and meningococcus meningitis. Of the others in this category, mumps, rubella, and varicella have such a low mortality that they cannot be considered here, and with poliomyelitis, the lack of any form of effective specific therapy would render its discussion of little value. The control of smallpox, although still the outstanding example of the efficacy of specific measures, belongs to a previous era.

The distribution of deaths in these common contagious diseases and their relative concentration during childhood, as well as the actual numbers of children dying from them in Continental United States, is reviewed in Table I.

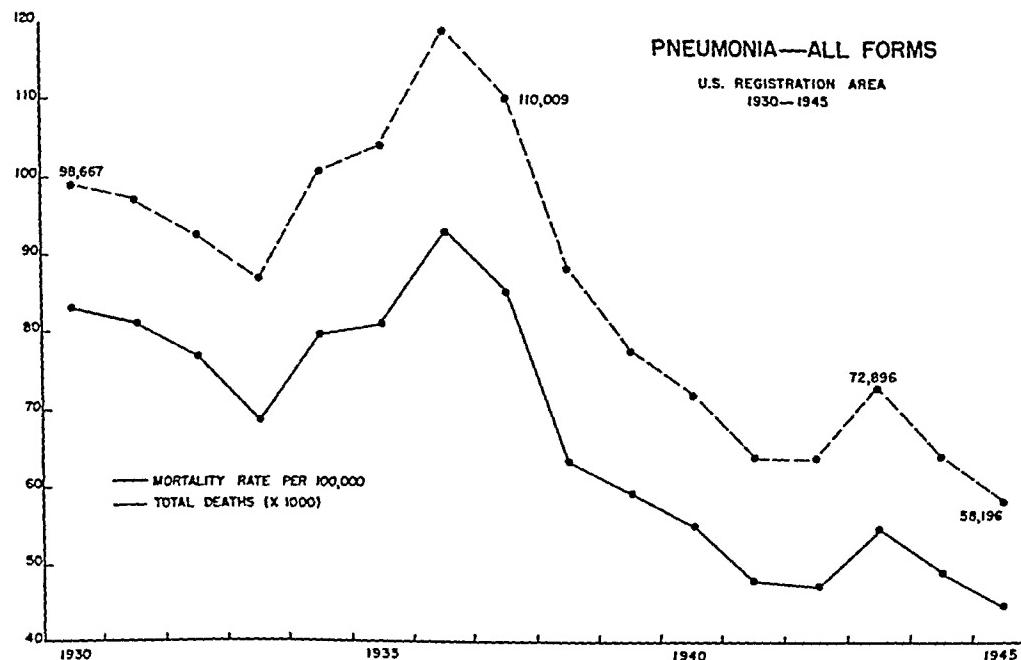
TABLE I. RELATION OF AGE TO MORTALITY OF COMMON CONTAGIOUS DISEASES AND THEIR RELATIVE FREQUENCY AS A CAUSE OF DEATH

DISEASE	PER CENT OF ALL DEATHS		TOTAL DEATHS UNDER 15 YR. 1941 TO 1945
	UNDER 5 YR.	UNDER 15 YR.	
Whooping cough	96	—	12,937*
Measles	67	87	6,075
Diphtheria	60	90	5,782
Epidemic meningitis	35	55	3,806
Scarlet fever	40	75	1,387

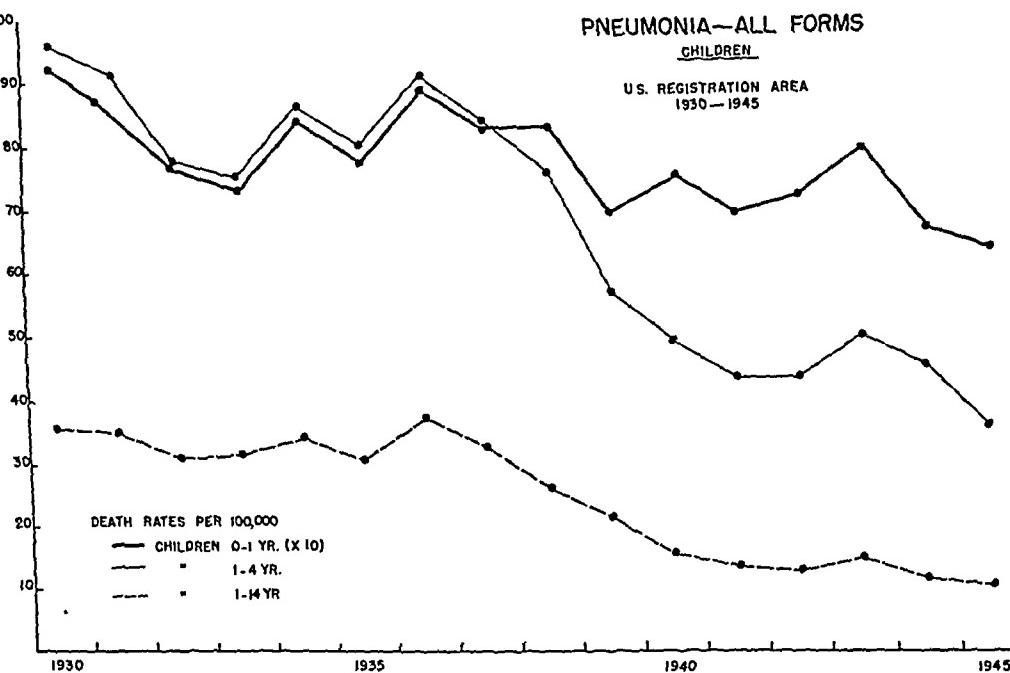
*Under five years.



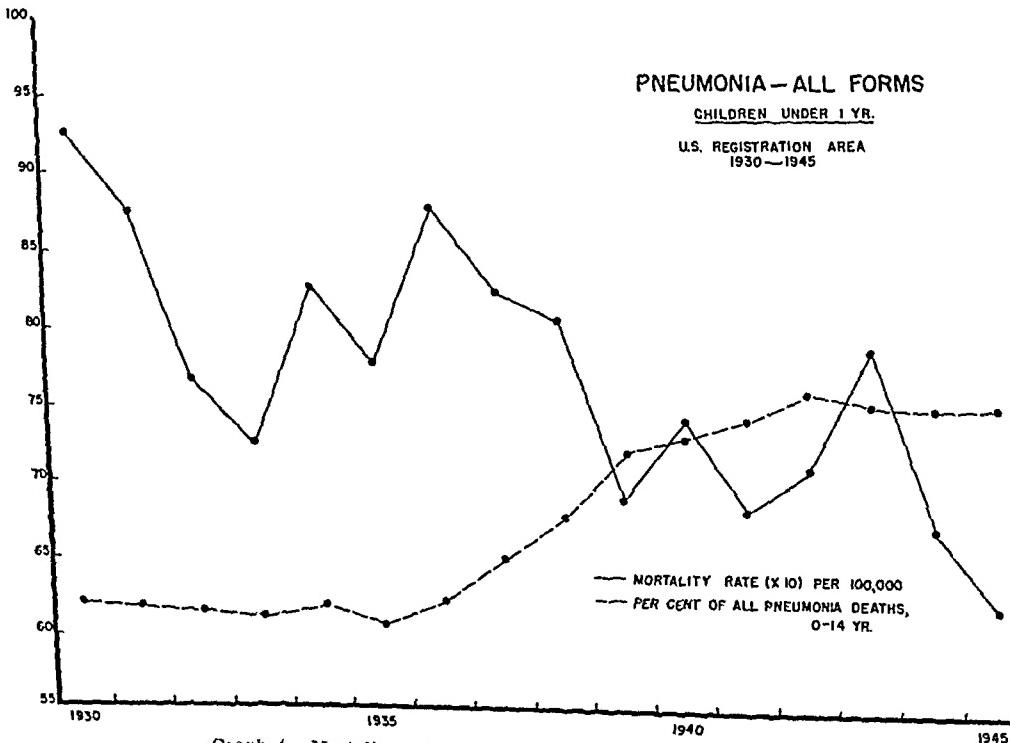
Graph 1.—Total deaths and mortality rate for infectious and parasitic diseases.



Graph 2.—Deaths and mortality rate, pneumonia.



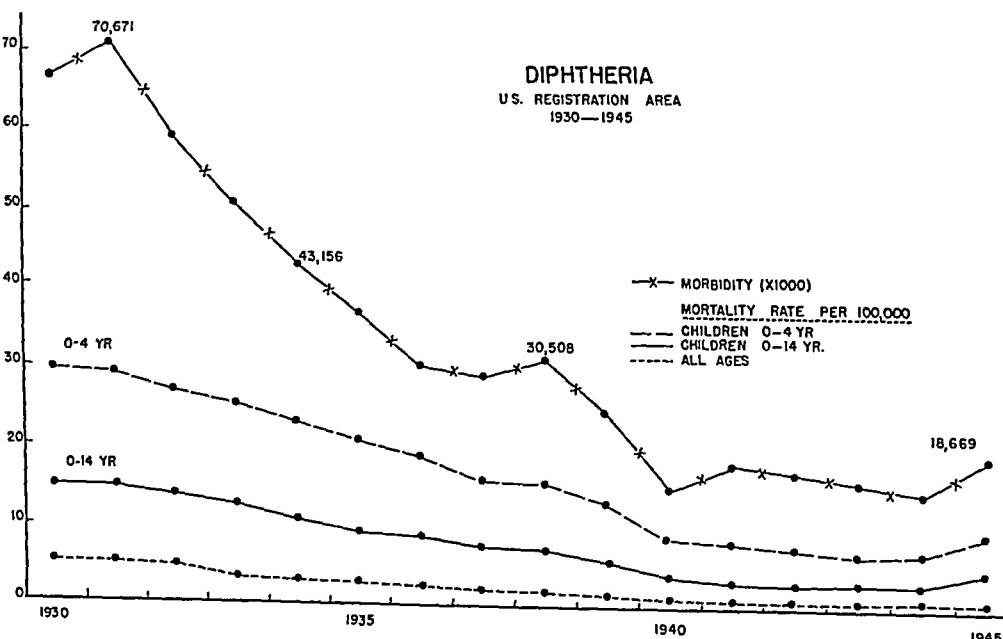
Graph 3.—Death rates, pneumonia in children.



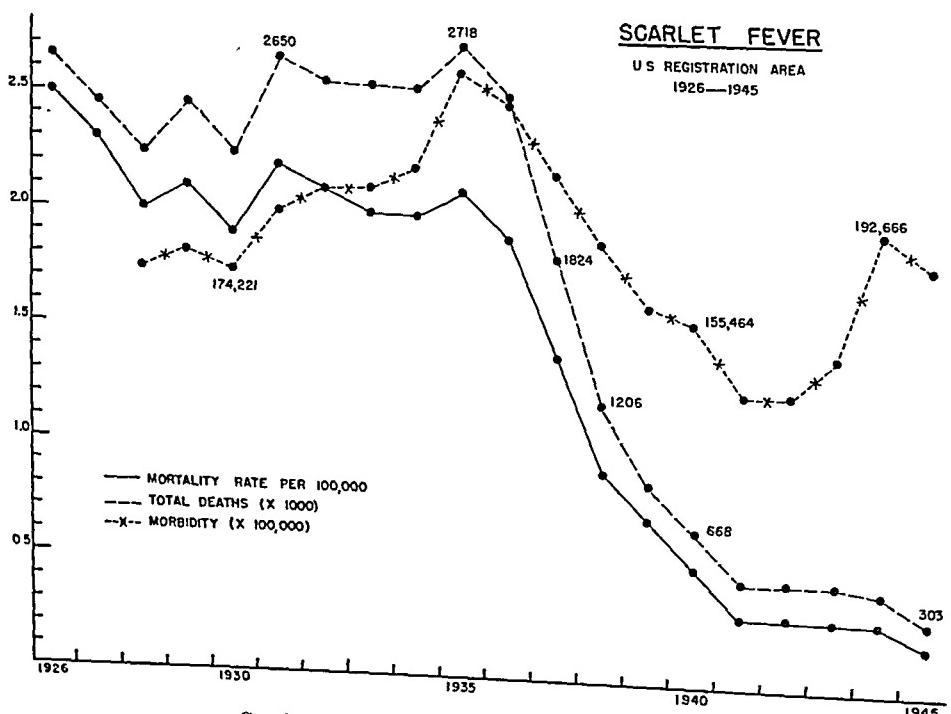
Graph 4.—Mortality rate, pneumonia in children 0 to 1 year of age.

Whooping cough leads the list with almost all of its deaths in younger children, and in each of the others more than one-half of the deaths occurred during childhood, while in measles and diphtheria the proportion is much higher. In the five-year period from 1941 to 1945, almost 30,000 children died from them, or a combined annual mortality rate of somewhat over 25 per 100,000. Possibly particular attention should be called to the fact that in this five-year period diphtheria, a disease for which specific measures of prophylaxis are most effective and which many believe to be now under control, still caused almost as many deaths in children as measles, and more than meningococcus meningitis and scarlet fever combined. At this point let us review in more detail the records of diphtheria and the effect of specific therapy in recent years.

Diphtheria.—To recount briefly and in general terms the well-known history of specific therapy on diphtheria, it is only necessary to state that in the early part of this century the general mortality rate for the disease was more than 20 per 100,000. The rate in children under 14 years was 60, and that in children under 5 years was more than 120 per 100,000 annually. With the increasing use of antitoxin in therapy, the mortality fell gradually but continuously until by the early 1920's the general rate had reached about 15 per 100,000 although there were still reported more than 100,000 cases annually with over 10,000 deaths, most of them in children. It was about this time that specific prophylaxis with toxin-antitoxin was started, and a few years later toxoid was introduced. Following its more general use, the effect on both the morbidity and mortality has been increasingly evident in the past two decades. In all years prior to 1935, diphtheria caused more deaths than any of the other common contagious diseases. The more recent course of the disease is shown in Graph 5, and it will be noted during the years 1930 to 1945 that there was a steady decrease in reported cases to a level of about 15,000 annually after 1940. The general mortality rate (shown in the lowest dotted line), which had reached 5 per 100,000 in 1930, fell to 1 per 100,000 by 1940. A somewhat more accurate picture of its severity is obtained, however, by noting that the mortality rate in children under 5 years, even in 1930, was 30 per 100,000 and that by 1945 this had fallen to about 7, while the decrease in mortality rate of children under 15 years was from 15 to 3 in this period. In all groups the mortality rate fell to about one-fifth of its previous level, although slightly less in younger children. Diphtheria is, therefore, one of the striking modern examples of the effect on a large population of specific therapy, since no doubt exists that the results in the period shown are attributable almost entirely to specific prophylactic vaccination. However, it must be pointed out that in recent years the excellent effect on the morbidity and mortality of diphtheria has become much less apparent and, since 1940, the curves have leveled off with relatively slight tendency to fall further. It is obvious that a disease which needs only the wide application of known and easily applied specific preventive measures to eradicate it, and which still has an incidence of almost 15,000 cases annually with well over 1,000 deaths yearly in children over a period of years, cannot be regarded with complacency.



Graph 5.—Morbidity and mortality rate, diphtheria.



Graph 6.—Morbidity and mortality, scarlet fever.

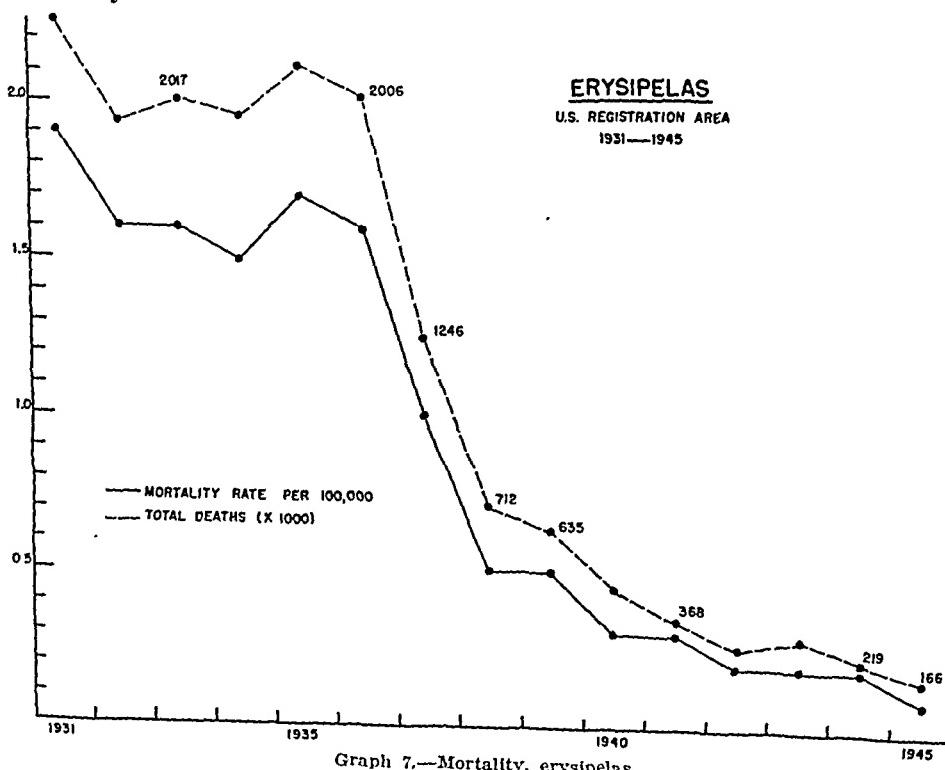
Possibly it is only necessary to stress the fact that the progress in the control of diphtheria has almost reached a standstill and that it remains a definite menace to life in children, in order to emphasize the necessity of increased efforts at more widespread active specific prophylaxis. No new methods in control are apparently needed, since those available are quite effective, but the greater utilization of the present control methods is needed.

Scarlet Fever.—Next let us observe the mortality course of scarlet fever over a twenty-year period from 1926 to 1945 in Graph 6, on which is shown also the reported cases. Although the figures are those of the mortality in all ages, 75 per cent of all deaths in scarlet fever were in children, so that the actual mortality rate in childhood is somewhat greater than shown in the diagram. It will be noted that from 1926 to 1937, the deaths (shown in the broken line) ranged around 2,500 annually with a general mortality rate (the solid line) of just above 2 per 100,000. It was during this time that specific antiscarlatinal serum had some vogue in therapy, although it is doubtful if it was used on a wide scale. Certainly no striking effect on mortality is evident until 1937, after which the total deaths fell rapidly and, since 1941, range only around 400 annually with the mortality rate around 0.3. The number of reported cases of scarlet fever (the broken line with a cross) also showed some decrease in the early part of this period although the rise to over 192,000 in 1944 without a corresponding increase in mortality indicates that the fall in deaths is not related to a decreased incidence. The effect of the sulfonamides on streptococcal disease has been abundantly demonstrated, although the degree of its reflection on the general mortality of clinical scarlet fever is surprisingly gratifying.

Erysipelas.—Since scarlet fever is no longer to be considered a specific disease but as one of the clinical entities in the group of hemolytic streptococcal infections, it is of interest in this connection to consider another clinical type of streptococcal disease, viz., erysipelas. Early in the use of sulfonamide therapy it was evident that this infection was conspicuous in showing a prompt and constant curative effect from such drugs. In Graph 7 is shown the mortality curve of this infection and its agreement with that of scarlet fever is apparent. From an average of 2,000 annual deaths before 1937, the mortality fell rapidly and continuously to reach a point of approximately 10 per cent of the previous level. So far as children are concerned, approximately one-third of all erysipelas deaths were in children previous to 1937. After this time this percentage fell rapidly, so that in the most recent three years shown, the proportion of erysipelas deaths in children was only about one-tenth. The effect of specific therapy, therefore, has been strikingly more pronounced in children than in adults. Possibly it is of special interest to mention that deaths from erysipelas under one year of age which ranged from 500 to 700 annually in the years before 1937, averaged only 30 annually in the last five years shown.

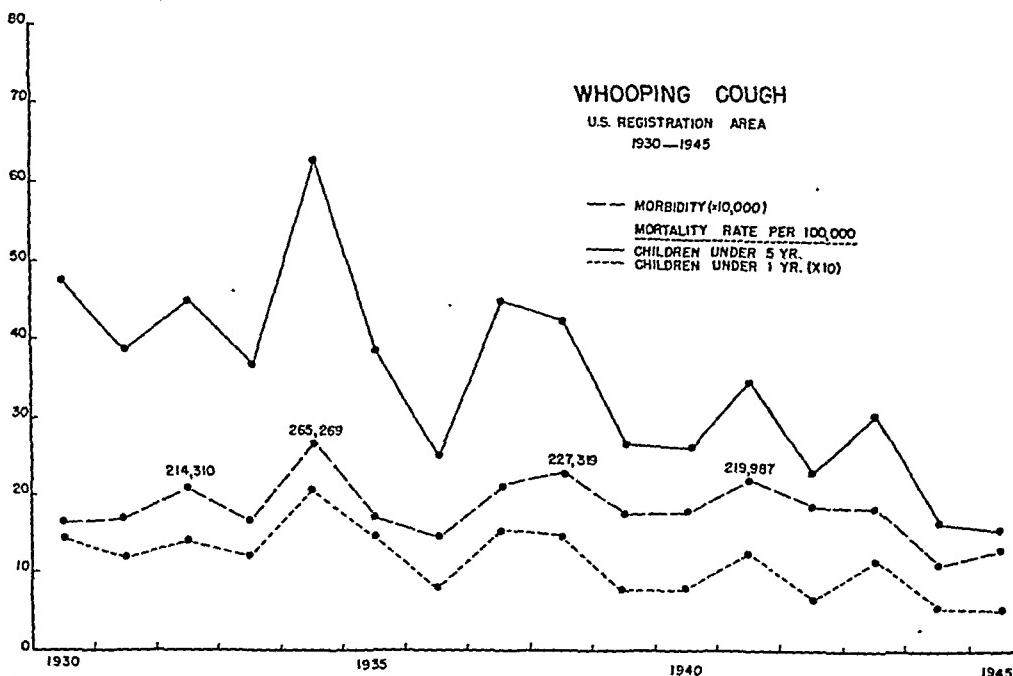
Exact information on the general incidence of erysipelas during this period is not available since it is not among the reportable diseases, but in the past ten years it has been apparent that the number of cases seen has de-

creased very strikingly so that the infection which previously was moderately common is now relatively rare. The mortality fall in erysipelas, as a result of specific therapy, is, therefore, closely associated with a decreased incidence of the clinical disease and in this respect differs somewhat from that noted in the case of scarlet fever. The possible reasons for this appear to be concerned with the nature of erysipelas infection and warrant brief comment. In a previous study of a number of children with erysipelas by clinical and cultural methods, it was found that in a very high proportion of idiopathic cases, the patients had an associated acute upper respiratory infection and there is considerable evidence that idiopathic erysipelas is usually a secondary skin inoculation of streptococcal disease already present in the upper respiratory tract. This view is further supported by the frequency of erysipelas around the face and head. The increasing and widespread use of sulfonamides for all upper respiratory disease and the arresting effect of this form of specific therapy on all streptococcal infection may well be an important factor in the decreased incidence of clinical erysipelas, as well as on its mortality.



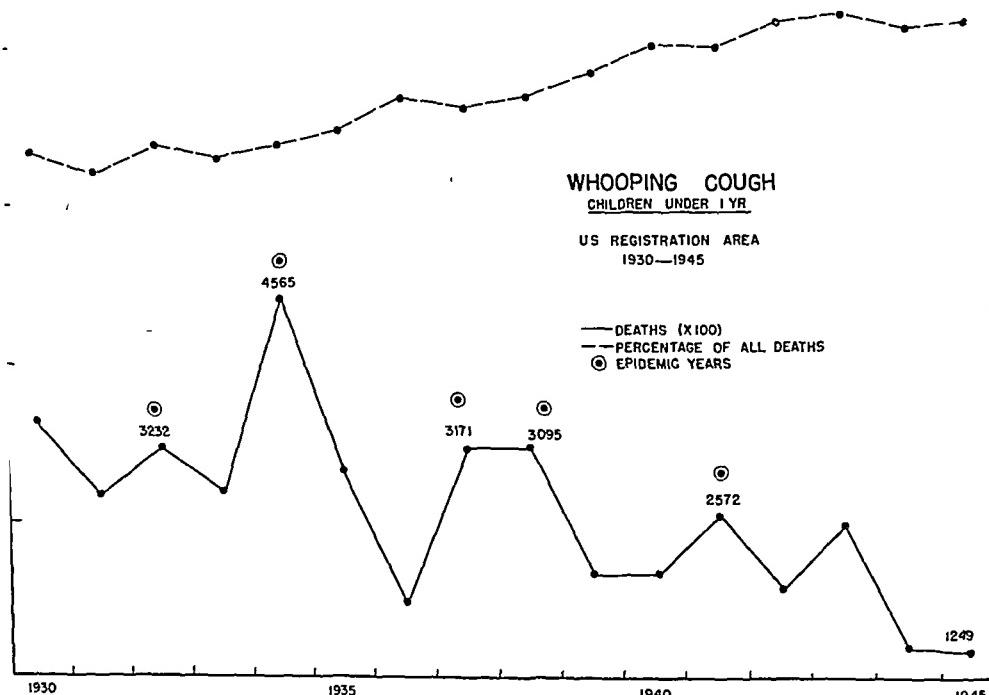
While the striking effect of specific therapy in the form of sulfonamides on the mortality of streptococcal disease is so obvious as to require no further discussion of its causal relationship, let us next consider another of the common contagious diseases in which the effect of specific therapy is less marked, although apparently definite.

Whooping Cough.—As has been mentioned, whooping cough in 1935 displaced diphtheria as the chief cause of death among the common communicable diseases. Over many years 95 per cent or more of the deaths have been in children under 5 years of age so that we can limit the observations to this age group. Actually, however, over 99 per cent of all deaths occur in children under 15 years of age. In diseases in which there are marked epidemic fluctuations in morbidity with corresponding variations in the mortality, there are obvious difficulties in the demonstration of effects of specific therapy by mortality figures alone unless these effects are of more than slight degree. This is illustrated in Graph 8 in which the mortality rate (the upper solid line) of whooping cough is shown in children under 5 years. The morbidity curve of reported cases (very greatly reduced) is drawn (as a broken line) to illustrate the considerable variations in incidence. If one considers that an annual

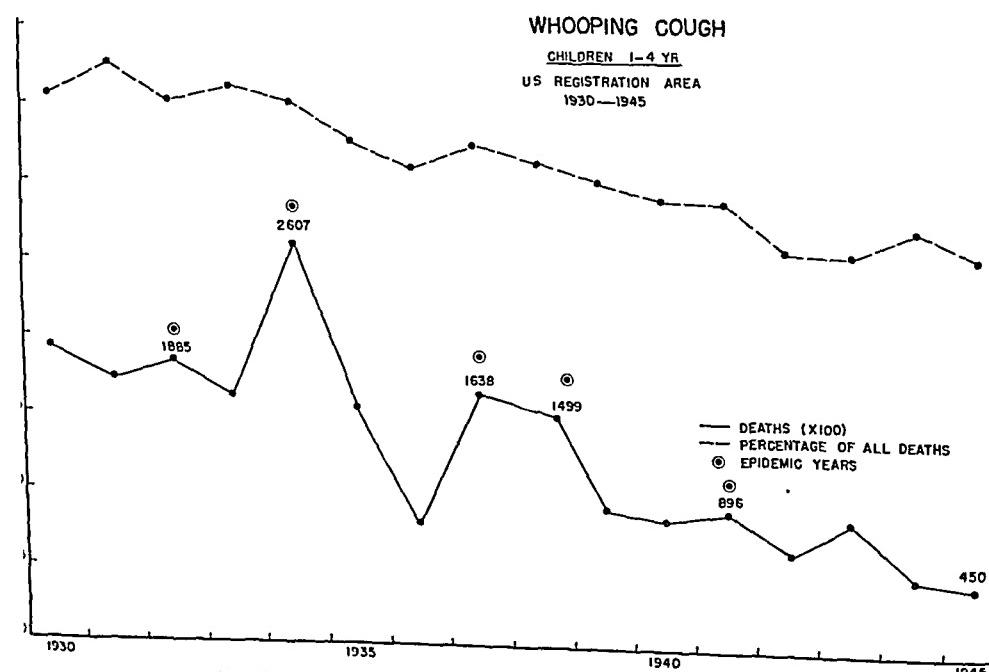


Graph 8.—Morbidity and mortality, whooping cough.

reported morbidity of more than 200,000 cases constitutes an epidemic year, it will be seen that 1932, 1934, 1937, 1938, and 1941 were such years of greatly increased incidence. The mortality rate curve (the upper solid line) shows considerable variations coincident with the morbidity, but, after 1937, it is evident that the peaks of the mortality rate in 1941 and 1943 are definitely lower than in previous years of increased incidence. More striking is the greatly decreased mortality in 1944 and 1945, and, from the figures available from the Public Health reports, this decrease persisted in 1946 and was then



Graph 9.—Mortality of whooping cough, 0 to 1 year of age.



Graph 10.—Mortality of whooping cough, 1 to 4 years of age.

even considerably lower than in 1945. Although the figures of the past two years are not yet available, the record shown in the chart of increasing and persistent fall in general national whooping cough mortality in the past decade is of a degree that leaves little doubt of great improvement.

The increasing use of prophylactic whooping cough vaccination may be considered in relation to the observed incidence of the disease, since one would expect this specific measure would have an effect primarily on the total morbidity and only secondarily on the mortality. In the reported incidence (the middle broken line), it is to be noted that only in 1944 and 1945 is there a decided decrease but it may be added that this decrease is still maintained in the two following years. This decline strongly suggests that active pertussis immunization had indeed been sufficiently widespread to affect the general incidence of the disease.

In the lowest curve (the dotted line) is plotted the mortality rate in infants under one year of age in which the annual variations follow those of the morbidity curve but with relatively slight reduction in height. This mortality in the first year presents some interesting features as compared to that of children 1 to 4 years of age and in the next chart (Graph 9) the curve of total annual deaths under one year is again shown. The decrease in the number of deaths and in the height of the peaks in epidemic years after 1938 is evident although slight. Most interesting, however, is the relative increase in whooping cough deaths in this early age group. In the upper curve, that of all whooping cough deaths, about 60 per cent occurred in the first year during the early 1930's while the proportion rose rapidly after 1938 to reach more than 70 per cent of all pertussis deaths. It is apparent that some factors concerned with the decline in mortality were operating more effectively at other ages than in young infants during this period. This relative increase in infant deaths is in part explained by noting the whooping cough mortality curve of children in the 1- to 4-year age group during this period as shown in Graph 10. Here the total annual deaths show a very decided reduction in the years subsequent to 1938, notably in the epidemic year of 1941. In addition to the absolute fall in deaths there was, as noted by the upper curve, a considerable relative decrease in the percentage of all pertussis deaths to the same degree that younger infants had shown a relative increase.

Two factors which might be concerned in explaining this discrepancy suggest themselves. First, the possibility that in recent years the relative incidence of pertussis in children over one year of age has been decreased by prophylactic vaccination. Since the common practice has been to employ this measure during the latter part of the first year, one might expect that this would result in a relatively increased incidence and consequent higher mortality in younger infants. No age incidence figures are available to support this suggestion, although it seems somewhat unlikely that it would entirely explain the difference in mortality noted. In this connection, and because whooping cough mortality has more and more become primarily a problem of the first year of life, the question of earlier specific immunization must be seriously considered. Recent studies have shown that active immunization

in early infancy is as effective as in older babies and there seems no longer any justification for delay in this procedure, since the urgent need for early protection is only too apparent. The second factor concerned in the relatively increased mortality from pertussis in the first year may be related to the effect of specific therapy on bronchopneumonia to which whooping cough mortality is largely due. Reference has been made previously to the fact that the recent decrease in general mortality from common contagious diseases was coincident with the increasing use of specific therapy with sulfonamide drugs. In whooping cough, as will be seen later in measles, this fall in mortality is much more evident and definite in children over one year of age than it is in younger infants. This is quite analogous to what has been pointed out in deaths from pneumonia unassociated with these diseases in children, and suggests strongly that the discrepancy is largely due to the pneumonia therapy. Since there is no evidence that sulfonamides are less effective in early infancy than in later life, it appears likely that the difficulty in administration of these drugs by mouth in adequate dosage to young infants has been an important consideration. All are familiar with these difficulties and with the fact that in hospital practice with very ill young infants, adequate drug and fluid administration is often possible only by parenteral injections. This procedure is only rarely practicable elsewhere and consequently limits effective therapy in this group in many instances. In this connection, also, must be mentioned the fact that staphylococci are several times as frequent as a cause of pneumonia and of empyema during early infancy than later. Since these infections are especially virulent and relatively resistant to sulfonamide therapy, it is possible that at least part of the increased number of deaths in the first year may be related to them. If the foregoing hypothesis is true, a considerable improvement is to be expected in mortality in young infants in the period subsequent to that shown, by the substitution of penicillin therapy in such cases, especially in younger infants with pneumonia. This antibiotic is apparently equally effective, can be given even in small infants readily, and has an additional advantage over sulfonamides of the ability to control staphylococcus infections.

It is true that young babies suffer more severely from all infections than older children, and we have become accustomed to the view that they have an inherent lack of resistance and a higher mortality than that seen in later life. It would be, however, unwise to adopt such a fatalistic attitude about mortality in early infancy without making every effort to obtain the maximum effect of all specific measures of proved value in this early age group. As has been suggested, there is evidence that this has not always been sufficiently emphasized.

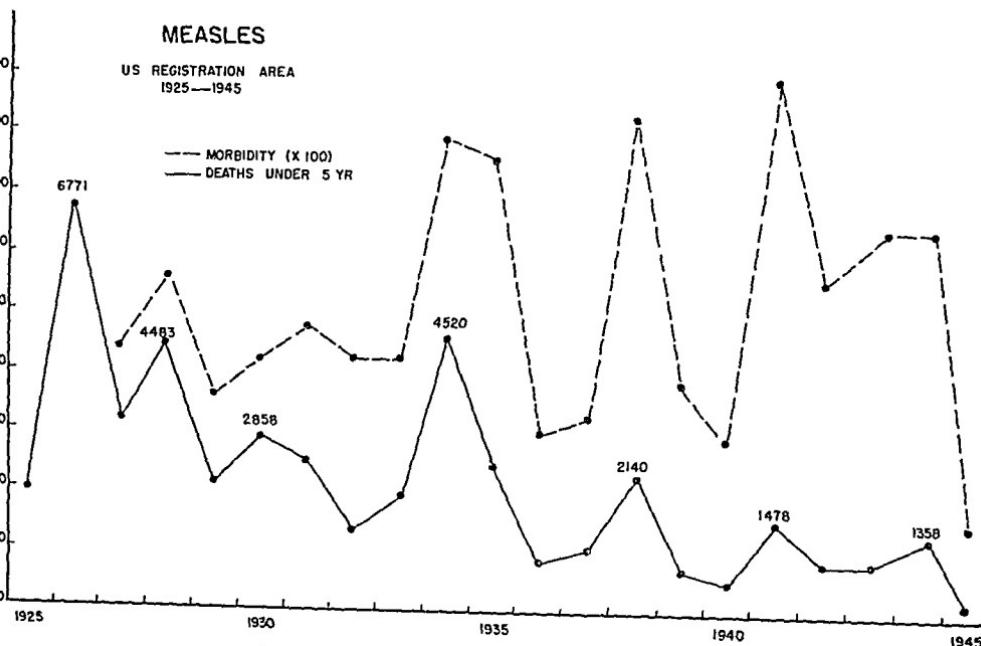
Measles.—The next mortality figures to be considered are those of measles, in which approximately one-half of all deaths occur in the first two years of life with two-thirds under the age of 5 years, and these proportions remain relatively constant in each year. The actual number of deaths and, of course, the mortality rate, may vary a great deal annually depending on the variations in incidence. The tabulation in Graph 11 shows those variations in a

twenty-year period from 1925 to 1945, and the relation of the reported case morbidity to the mortality. The actual number of deaths in children under 5 years is shown for the various years and is a little more impressive than the mortality rate curve, although the latter is almost identical in outline. It will be noted that, for example, 1928, 1934, 1935, and 1941-1944 were epidemic years during which more than twice the number of cases were reported than at other times. The reported incidence during these epidemics exceeded 500,000 cases annually and at times reached around 800,000 as compared with that of 200,000 to 400,000 in the intervening years. The annual incidence of deaths follows a curve roughly corresponding that of the morbidity in the years prior to 1937, but after that time there is a very definite decrease in the number of deaths. Even the peaks during the epidemic years of 1938 and 1941 show less than one-half the deaths in previous epidemic years, and are even lower than in many of the previous non-epidemic years. The extremely low morbidity and mortality in 1945 is unusual, and in the year following, from Public Health Reports, measles was again epidemic with almost 700,000 cases but with only about 1,200 deaths.

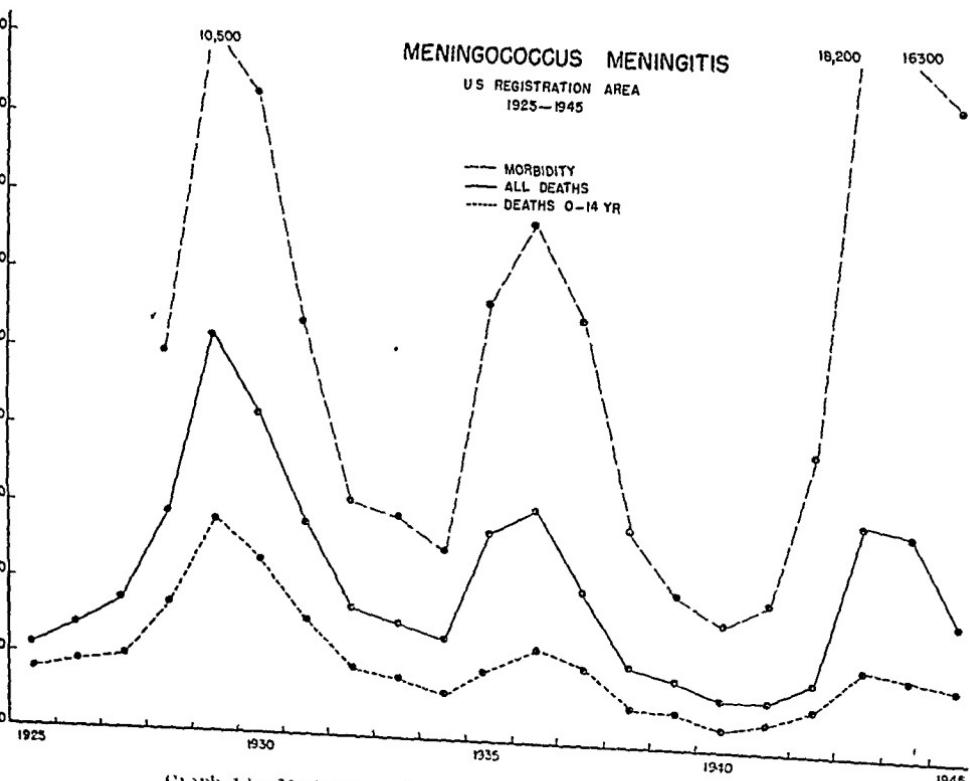
Since by far the most important cause of death in measles, as in pertussis, is a secondary pneumonia, it appears likely that the decrease in measles deaths since 1937 is largely attributable to a diminished mortality from pneumonia in the same manner as had been suggested in the case of whooping cough, and is coincident with the increased use of specific sulfonamide drug therapy. In this connection it is of some interest that the number of deaths annually from measles in the second year of life was considerably greater than that during the first year up to and including 1938. This was to be expected since measles is less common during the first year because of the well-known inherited immunity to the disease during the early months of life. Since 1938, however, there have been more deaths annually in the first year than in the second. Although in both age groups the measles mortality decreased, the agents affecting the decrease operated less effectively on infants under one year, as was apparent also in pneumonia and in whooping cough. The greater ease of penicillin therapy as compared with sulfonamide drugs in the treatment of these younger infants may be expected to show an increasingly favorable response in subsequent years, as was suggested in the case of whooping cough.

One form of specific therapy to be mentioned in relation to measles is the use of immune globulin and gamma globulin, although the effect of these agents on the mortality of the disease is somewhat difficult to estimate. Since the period of ready availability of gamma globulin was subsequent to the period reported here, probably no evidence of the use of these agents could be expected in the mortality data under consideration.

Meningococcus Meningitis.—In considering meningococcus meningitis, the last of the common contagious diseases for which the effect of specific therapy on mortality is to be reviewed, several features must be taken into account. Although this disease is the least prevalent, the variations in incidence between epidemic periods and non-epidemic years are greater, and the case fatality

MEASLESUS REGISTRATION AREA
1925—1945— MORBIDITY (X 100)
— DEATHS UNDER 5 YR

Graph 11.—Morbidity and mortality, measles

MENINGOCOCCUS MENINGITISUS REGISTRATION AREA
1925—1945— MORBIDITY
— ALL DEATHS
— DEATHS 0-14 YR

Graph 12.—Morbidity and mortality, meningococcus meningitis

rate is higher than in any of the other diseases considered. Certain general statements may be made about specific therapy of this infection, which can be divided into two periods: first, that with antimeningococcus serum which was in common use from early in the present century; and second, chemotherapy with sulfonamide drugs starting in 1937-1938. With serum therapy no doubt exists that under favorable conditions and with its use early in the infection in hospitals there was a considerable reduction in mortality. No data are available, however, for analysis of the effect of this treatment on the general mortality of the disease, although it still remained high. With the advent of the sulfonamide drugs, however, all clinics noted a very striking fall in mortality. A single example will illustrate this and is typical of the experience in most hospital observations. At the St. Louis Children's Hospital during the years 1912-1937, in 222 children under 15 years admitted in various stages of meningococcus meningitis and treated by serum therapy the case fatality was 40 per cent, while in 135 children admitted after 1937 and treated with sulfonamide drugs the case fatality was only 5 per cent. The general incidence and mortality of the disease over a twenty-year period is shown in Graph 12, in which they are tabulated in thousands annually. Here the wide variations between epidemic periods and other years are evident, with a three- to tenfold epidemic increase. It is of interest that in all years prior to 1941, the actual number of deaths was from 40 to 50 per cent of the cases reported, while after this the deaths averaged only about 20 per cent of the cases or about one-half of those in the previous period. In the lowest (dotted) line is shown the annual mortality in children under 15 years which forms a similar curve. In most years the proportion of childhood deaths is about 55 per cent of the total mortality but it is of some interest that during the epidemic of 1935-1936 and again in 1943-1944 this percentage of children's deaths was from 10 to 15 per cent lower, so that relatively many more deaths occurred in adults than in children. No data are available to explain this difference. It is possible that a higher incidence of the disease occurs in adults during epidemics since there is no evidence that therapy is more effective in older persons than in children.

Although the decrease in the general mortality level reached in recent years is gratifying, it is somewhat disappointing when compared with that possible in the larger clinics with modern treatment. One might attempt to explain this discrepancy in part by considering two possible factors which may interfere with more general application of therapy. The first concerns the difficulty in early diagnosis in certain cases of meningitis, especially in infancy, because of the absence of classical signs of meningeal irritation. All pediatricians are familiar with the frequency with which the diagnosis of meningitis is made only after lumbar puncture, and that the value of this diagnostic measure in unexplained febrile illnesses is apparently not widely appreciated since many such infections are still admitted to hospitals without the diagnosis having been made. The second factor is related to the difficulties in administration of adequate sulfonamides by mouth in infants and at times

in older children severely ill with meningitis and requiring parenteral therapy in a manner similar to that discussed in the therapy of young infants with whooping cough pneumonia. Since 1945 the replacement of penicillin therapy for sulfonamides in such cases may well have a considerable effect on the mortality of this infection. Both of these factors are not important in most hospital practice but may have a bearing on the mortality of the disease elsewhere.

SUMMARY

To summarize briefly the effects of specific therapy on the common contagious diseases as shown by the recorded general morbidity and mortality in the United States, the following may be emphasized:

1. Both the incidence and the deaths from diphtheria have shown striking reductions coincident with the increasing use of specific active immunization with toxoid. The fact that, in recent years, this reduction in morbidity and mortality has reached a halt without further downward progress, suggests that a new emphasis must be placed on the necessity for continued and more widespread active immunization of children. This is especially true since diphtheria still causes a large number of preventable deaths.

2. Scarlet fever and other streptococcal infections including erysipelas have shown a rather abrupt and striking fall in mortality as a result of sulfonamide therapy. Clinical scarlet fever, although still moderately prevalent, when treated by modern methods of specific therapy with sulfonamide drugs and penicillin has reached such a low mortality as no longer to constitute a serious menace to life in children.

3. In whooping cough, there is some evidence in the years subsequent to 1943 that the incidence of the disease is decreasing as a result of specific prophylactic vaccination, since fewer cases were reported in the years 1942 to 1947 than in any previous ones. The fact that more than 70 per cent of all pertussis deaths occur in the first year of life, however, emphasizes the desirability of earlier active immunization than now generally employed. There was an easily demonstrable fall in general mortality in whooping cough coincident with the period of increasing use of specific sulfonamide drugs therapy. This was apparently due to the effect of such treatment on the associated bronchopneumonia, since a similar reduction in mortality occurred during this period in measles and in children with pneumonia not associated with these diseases. The mortality of infants in the first year of life was much less affected in both whooping cough and measles than in older children, possibly because of certain difficulties in the application of specific therapy in such young infants.

4. The general mortality of meningococcus meningitis has also shown a decided decrease due to specific sulfonamide therapy, although its maximum beneficial effect has apparently not been attained because of certain difficulties in diagnosis and in the application of adequate treatment. It is likely that the more common use of diagnostic lumbar puncture in febrile illnesses of ill-defined origin, and with the increasing use of penicillin for therapy in meningococcus meningitis, especially in younger children, the mortality will be still further reduced.

I hope that this review has clarified the results of specific therapy on the common contagious diseases of children in the past decade as reflected by their mortality in the nation. In all of these diseases the effect of specific measures has been definite and in some it has been most striking. Certainly the improvement has been greater in conservation of life in these diseases than in any previous similar period. It is still necessary, however, by precept and education to emphasize the need of wider application of methods already available in order to extend the help of these methods of therapy to all children so that the maximum benefit may be obtained. One can confidently hope that with more general use of newer forms of specific treatment, especially antibiotics, that still further progress will be apparent in the near future.

MORTALITY TABLES

The following tables give the statistical data from which the graphs were prepared. The mortality figures are from the annual reports of the Vital Statistics of the United States Bureau of the Census, and those of morbidity are from the Bulletins of the U. S. Public Health Service. Mortality rates per 100,000 on children were estimated on the 1930 census figures for years 1926 to 1935 and on 1940 census figures for years 1936 to 1945.

CENSUS FIGURES—CHILDREN—CONTINENTAL UNITED STATES

	ALL PERSONS	0-1 YR.	0-5 YR.	5-9 YR.	10-14 YR.	0-14 YR.
April 1, 1930	122,773,046	2,190,791	11,444,390	12,607,609	12,004,877	36,056,876
April 1, 1940	131,954,144	2,020,174	10,541,524	10,684,622	11,745,935	32,972,081

DEATHS FROM INFECTIOUS AND PARASITIC DISEASES AND FROM PNEUMONIA (U. S. REGISTRATION AREA)

YEAR	POPULATION (U. S. REGIS- TRATION AREA)	INFECTIOUS AND PARASITIC DISEASES		PNEU MONIA, ALL FORMS	
		DEATHS	MORTALITY RATE PER 100,000	DEATHS	MORTALITY RATE PER 100,000
1930	118,560,800	162,326	137	98,667	83
1931	119,421,000	163,166	137	96,974	81
1932	120,122,000	154,320	131	92,474	77
1933	125,578,763	155,821	124	86,949	69
1934	126,373,773	148,124	117	100,573	80
1935	127,250,232	146,840	115	104,395	81
1936	128,053,180	148,798	116	119,378	93
1937	128,824,829	149,959	116	110,009	85
1938	129,824,939	119,685	90	87,923	64
1939	130,879,718	125,526	96	77,633	59
1940	131,954,144	119,755	93	72,368	55
1941	133,060,045	119,320	90	63,935	48
1942	133,770,500	102,596	76	63,630	48
1943	133,996,319	111,160	81	72,896	54
1944	132,552,005	105,769	80	64,484	49
1945	131,973,774	92,933	70	58,196	44

**DEATHS FROM PNEUMONIA, ALL FORMS, IN CHILDREN UNDER 15 YEARS OF AGE
(U. S. REGISTRATION AREA)**

YEAR	ALL UNDER 15 YR.		UNDER 1 YR.			1-4 YR.		1-14 YR.	
	DEATHS	RATE	DEATHS	%	RATE	DEATHS	RATE	DEATHS	RATE
1930	32,176	89	19,948	62.0	921	8,862	95.7	12,228	36.0
1931	30,577	85	18,897	61.8	874	8,422	90.7	11,680	34.7
1932	27,019	75	16,590	61.4	768	7,221	77.8	10,429	30.8
1933	25,447	71	15,631	61.4	724	6,914	74.5	10,816	31.9
1934	29,364	82	17,900	61.0	829	8,085	86.0	11,464	33.9
1935	26,873	75	16,599	61.8	768	7,339	79.1	10,274	30.3
1936	29,256	88	17,749	60.6	878	7,665	90.0	11,507	37.2
1937	26,648	81	16,562	62.1	820	7,098	83.3	10,086	32.6
1938	24,727	75	16,014	64.8	793	6,151	74.5	8,710	28.1
1939	20,388	62	13,786	67.6	682	4,682	56.8	6,602	21.3
1940	20,452	62	14,881	72.8	737	4,097	48.1	5,571	18.0
1941	18,578	56	13,687	73.7	678	3,688	43.3	4,891	15.8
1942	19,004	58	14,333	75.4	709	3,562	43.2	4,671	15.1
1943	21,200	64	15,819	74.6	783	4,055	49.0	5,381	17.4
1944	18,116	55	13,500	74.5	668	3,537	44.5	4,616	11.7
1945	17,003	52	12,661	74.5	627	3,213	37.7	4,342	10.8

DIPHTHERIA (U. S. REGISTRATION AREA)

YEAR	ALL PERSONS			DEATHS IN CHILDREN UNDER 5 YR.			DEATHS IN CHILDREN UNDER 15 YR.		
	MOR-BIDITY	DEATHS	RATE	NUMBER	%	RATE	NUMBER	%	RATE
1930	66,576	5,822	4.9	3,428	58.9	30.0	5,356	92.0	14.9
1931	70,671	5,738	4.8	3,388	59.1	29.6	5,275	91.9	14.6
1932	59,784	5,418	4.5	3,135	57.9	27.4	4,959	91.5	13.8
1933	50,462	4,937	3.9	2,951	59.8	25.8	4,495	91.0	12.5
1934	43,156	4,159	3.3	2,582	62.1	22.6	3,774	90.7	10.5
1935	36,564	3,901	3.1	2,349	60.2	20.5	3,504	89.8	9.7
1936	30,018	3,065	2.4	1,952	63.7	18.5	2,748	89.7	8.3
1937	28,536	2,637	2.0	1,657	62.8	15.7	2,353	89.2	7.1
1938	30,508	2,556	2.0	1,594	62.4	15.1	2,308	90.3	7.0
1939	24,053	1,997	1.5	1,297	64.9	12.3	1,791	89.7	5.4
1940	15,536	1,457	1.1	911	62.5	8.6	1,285	88.2	3.9
1941	17,678	1,293	1.0	833	64.4	7.9	1,159	89.6	3.5
1942	16,260	1,273	1.0	819	64.3	7.8	1,132	88.9	3.4
1943	14,811	1,196	0.9	721	60.2	6.8	1,045	87.3	3.2
1944	14,150	1,145	0.9	727	63.5	6.8	1,041	90.9	3.2
1945	18,669	1,598	1.0	934	58.4	8.9	1,405	87.9	4.3

SCARLET FEVER (U. S. REGISTRATION AREA)

YEAR	ALL PERSONS			CHILDREN UNDER 5 YR.		CHILDREN UNDER 15 YR.		
	MORBIDITY	DEATHS	MORTALITY RATE	DEATHS	%	DEATHS	%	MORTALITY RATE
1925	-----	2,762	2.7	1,187	43	2,160	78	6.0
1926	-----	2,662	2.5	1,169	44	2,143	81	6.0
1927	-----	2,440	2.3	1,049	43	1,944	80	5.4
1928	174,662	2,229	2.0	973	44	1,787	80	5.0
1929	182,634	2,468	2.1	1,080	44	1,919	78	5.3
1930	174,221	2,279	1.9	981	43	1,829	85	5.1
1931	200,607	2,650	2.2	1,127	43	2,096	80	5.8
1932	210,014	2,577	2.1	998	39	1,993	77	5.5
1933	212,395	2,516	2.0	987	39	1,986	79	5.5
1934	220,050	2,524	2.0	988	39	1,970	78	5.5
1935	260,962	2,718	2.1	944	35	2,010	74	5.6
1936	244,332	2,493	1.9	788	34	1,723	69	5.2
1937	228,887	1,824	1.4	693	38	1,288	71	3.9
1938	189,631	1,206	0.9	493	41	935	78	2.8
1939	162,897	853	0.7	332	39	614	72	1.9
1940	155,464	668	0.5	261	39	508	76	1.5
1941	126,988	454	0.3	176	39	343	75	1.0
1942	128,194	447	0.3	152	34	318	71	1.0
1943	142,622	451	0.3	127	28	294	65	0.9
1944	192,666	422	0.3	114	27	263	62	0.8
1945	175,378	303	0.2	66	22	179	59	0.4

ERYSIPelas (U. S. REGISTRATION AREA)

YEAR	ALL PERSONS		CHILDREN 0-1 YR.		CHILDREN 0-14 YR.	
	DEATHS	MORTALITY RATE	DEATHS	MORTALITY RATE	DEATHS	%
1925	2,455	2.4	719	32.0	882	35.9
1926	2,680	2.6	791	36.2	967	36.1
1927	2,567	2.4	776	35.4	937	36.5
1928	2,724	2.4	741	33.9	900	33.1
1929	2,887	2.5	780	35.6	947	32.8
1930	2,508	2.1	720	32.9	886	36.1
1931	2,275	1.9	638	29.1	787	34.6
1932	1,934	1.6	529	24.1	661	34.2
1933	2,017	1.6	562	25.7	674	33.4
1934	1,947	1.5	525	24.0	644	32.5
1935	2,106	1.7	572	26.5	701	33.3
1936	2,006	1.6	457	22.6	551	27.5
1937	1,246	1.0	270	13.4	331	26.6
1938	712	0.5	154	7.6	179	25.1
1939	635	0.5	107	3.3	135	21.1
1940	451	0.3	83	4.1	105	23.3
1941	368	0.3	54	2.7	70	21.7
1942	261	0.2	41	2.0	52	19.9
1943	281	0.2	24	1.2	34	12.1
1944	219	0.2	19	0.9	23	10.6
1945	166	0.1	14	0.7	17	10.0

WHOOPING COUGH (U. S. REGISTRATION AREA)

MEASLES (U. S. REGISTRATION AREA)

YEAR	ALL PERSONS			0-1 YR.		1-2 YR.		UNDER 5 YR.		
	MORBID-ITY	DEATHS	RATE	DEATHS	%	DEATHS	%	DEATHS	%	RATE
1925	2,404	2.3		667	27.7	784	32.6	1,944	81.2	18.4
1926	8,607	8.2		2,182	25.4	2,596	30.2	6,771	78.7	59.3
1927	441,349	4,433	4.1	1,037	23.4	1,189	26.8	3,244	73.2	28.4
1928	561,721	6,146	5.4	1,486	24.0	1,728	28.1	4,483	72.6	39.3
1929	366,056	2,923	2.5	646	22.1	827	28.3	2,134	73.0	18.7
1930	419,465	3,820	3.2	827	21.6	1,050	27.5	2,858	74.8	25.0
1931	474,549	3,576	3.0	766	21.1	968	28.2	2,570	71.9	23.0
1932	403,294	1,941	1.6	436	22.5	479	24.7	1,325	68.2	12.0
1933	400,894	2,813	2.2	576	20.5	728	25.9	1,934	68.8	17.0
1934	799,455	6,986	5.5	1,497	21.4	1,542	22.1	4,520	64.7	40.0
1935	743,856	3,907	3.1	798	20.4	861	22.0	2,440	62.3	23.0
1936	299,493	1,267	1.0	252	20.0	305	24.1	816	64.4	8.0
1937	321,510	1,501	1.2	332	22.1	378	25.2	1,026	68.3	10.0
1938	822,811	3,296	2.5	718	21.8	729	22.0	2,140	64.9	20.0
1939	403,317	1,174	0.9	297	25.4	235	20.0	741	63.1	7.0
1940	291,162	706	0.5	182	25.8	168	23.8	509	72.1	5.0
1941	881,529	2,279	1.7	604	26.5	436	19.1	1,478	64.9	14.0
1942	547,393	1,302	1.0	341	26.2	243	18.6	823	63.2	8.0
1943	633,627	1,301	1.0	318	24.5	273	20.9	853	65.6	8.0
1944	530,291	1,923	1.5	536	27.8	423	22.0	1,358	70.6	13.0
1945	146,002	307	0.2	91	29.6	67	21.8	214	69.7	2.0

MENINGOCOCCUS MENINGITIS (U. S. REGISTRATION AREA)

YEAR	ALL PERSONS			CHILDREN UNDER 5 YR.			CHILDREN UNDER 15 YR.			MORTALITY RATE
	MORBIDITY	DEATHS	MORTALITY RATE	DEATHS	%	DEATHS	%	DEATHS	%	
1925	---	1,095	1.0	565	51.6	777	71.0			
1926	---	1,413	1.3	623	44.1	913	64.6			2.6
1927	---	1,705	1.6	671	39.4	1,046	62.5			2.9
1928	4,996	2,923	2.6	982	33.6	1,715	58.7			4.8
1929	10,551	5,208	4.5	1,629	31.3	2,844	56.5			7.6
1930	8,384	4,211	3.6	1,291	30.7	2,313	54.9			6.4
1931	5,426	2,832	2.3	924	32.6	1,567	55.3			4.4
1932	3,099	1,677	1.4	571	34.0	962	57.4			2.7
1933	2,913	1,482	1.2	511	34.5	815	55.0			2.3
1934	2,500	1,272	1.0	439	34.5	708	55.7			2.0
1935	5,736	2,657	2.1	670	25.2	1,131	42.6			3.1
1936	6,729	3,020	2.4	727	24.1	1,296	42.6			3.9
1937	5,484	2,208	1.7	630	28.5	1,114	50.5			3.4
1938	2,788	1,024	0.8	384	37.5	565	53.2			1.7
1939	1,967	863	0.7	346	40.0	511	59.2			1.5
1940	1,638	694	0.5	292	42.1	399	57.5			1.2
1941	1,949	713	0.5	291	40.8	401	56.2			1.2
1942	3,816	981	0.6	329	33.5	446	45.4			1.3
1943	18,221	2,927	2.2	762	26.0	1,120	38.3			3.4
1944	16,315	2,812	2.1	815	29.0	1,194	42.1			3.6
1945	8,190	1,728	1.3	621	35.9	845	48.8			2.6

CHORIORETINOPATHY ASSOCIATED WITH OTHER EVIDENCE OF CEREBRAL DAMAGE IN CHILDHOOD

A SYNDROME OF UNKNOWN ETIOLOGY SEPARABLE FROM CONGENITAL TOXOPLASMOSIS

ALBERT B. SABIN, M.D., AND HARRY A. FELDMAN, M.D.*
CINCINNATI, OHIO

EVER since chorioretinitis and cerebral calcification were recognized as important manifestations in proved fatal cases of congenital toxoplasmosis, this disease came to be considered in differential diagnosis whenever one or the other of these signs was found, especially in association with other evidence of cerebral damage in childhood. In the past nine years many investigators in the United States,¹⁻⁵ and more recently also in Sweden,⁶ Holland,^{7, 8} and Italy⁹ have used the rabbit test for toxoplasma antibodies for the serologic "confirmation" of the diagnosis of toxoplasmosis. The diagnosis of congenital toxoplasmosis was made in surviving children with clinical manifestations similar to those encountered in the proved fatal cases of this disease when toxoplasma antibodies were found in the serum of both child and mother. However, since little was known about the development and persistence of this antibody, the diagnosis was occasionally also regarded as highly probable when only the mother's serum had antibodies and in some instances of chorioretinitis, or cerebral calcification, or both, even in the absence of antibodies. Expressions such as "clinically typical toxoplasmic chorioretinitis" or "clinically typical cerebral calcification" had begun to appear in the literature. Since chorioretinitis of unknown etiology in adults was not infrequently found to be associated with toxoplasma antibodies in the patient's serum, "toxoplasmic chorioretinitis" had become a clinical entity of some importance in ophthalmology. However, the rabbit neutralization test on which these conclusions were based presented many pitfalls. Thus, the specific antitoxoplasmic activity of a serum was highly thermolabile even at ordinary refrigerator temperatures¹⁰ and was rapidly lost on slight dilution. The test was, therefore, qualitative rather than quantitative; it was incapable of differentiating between the antibody response due to toxoplasmic infection of relatively recent date and that resulting from exposure to toxoplasma in the more distant past, or conceivably to some other agent containing a related antigen. Although there was good evidence that inapparent or clinically unrecognized toxoplasmic infection occurred in human beings, little or nothing was known about the incidence of toxoplasma antibodies in different age groups of the normal population.

*From The Children's Hospital Research Foundation and Department of Pediatrics, University of Cincinnati College of Medicine.

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*Senior Fellow, National Research Council.

The recent development of new immunologic methods has provided the means for considerable clarification of the problem. The new methods are the skin test in human beings,¹¹⁻¹³ the complement fixation test with chorioallantoic membrane antigen¹¹ rendered more specific by high-speed centrifugation,¹¹ and the *in vitro* dye test for the demonstration of toxoplasma neutralizing antibodies.¹⁵ In our experience, the skin test in human beings has proved useful only for crude population surveys and useless for diagnosis, because it was not infrequently negative in individuals with antibodies in the serum and the extent of the positive reactions was not correlated with the titer of antibodies. A recent survey in the Cincinnati area revealed that the number of "normal" people giving positive skin reactions to toxoplasma antigen and containing antibody in their serum rises gradually from zero in those under 5 years of age to over 65 per cent in middle age and beyond.¹³ It is not clear at this time whether this high incidence of antibody, usually of low titer, in the older members of the normal population is all due to inapparent or unrecognized infection with toxoplasma or to infection with an as yet unknown agent antigenically related to it. It is clear, however, that mere association with toxoplasma antibodies, and more especially antibodies of low titer, cannot be regarded even as presumptive evidence that certain obscure clinical conditions are etiologically related to toxoplasma. The recently developed *in vitro* dye test¹⁶ provides the most sensitive and quantitative means for measuring toxoplasma neutralizing antibodies, and, together with the improved complement fixation test,¹⁴ yields the most precise information that can be obtained at this time regarding the immunologic response to toxoplasmic infection. The dye test depends on the discovery that the cytoplasm of the toxoplasma loses its affinity for methylene blue and certain other basic dyes after it has combined with the specific antibody, which is heat-stable and has been acted on by a heat-labile, nonspecific, accessory factor present in small amounts in human serum. The dye test titer refers to the highest original dilution of a serum which, in the presence of a constant amount of accessory factor, is capable of depriving the cytoplasm of 50 per cent of the toxoplasma of its affinity for methylene blue at pH 11.0. In experimental animals the dye test antibody appears within three to five days after infection and reaches peak titers of 1:1,000 to 1:4,000 in ten to twenty-one days, while the complement-fixing antibody, as a rule, appears later. The data which have been accumulated thus far indicate that the same high titers occur in both clinically apparent and inapparent toxoplasma infections in human beings, and can persist at this high level for at least two to five years. The complement-fixing antibodies can also persist for this long period in human beings,¹⁴ and it is, therefore, of interest that the low-titer neutralizing antibodies encountered so often in the normal population are much less frequently associated with complement-fixing antibodies.

During the past year we applied the dye test, and in most instances also the complement fixation test, to the study of sixty children with various manifestations suggestive of congenital or neonatal cerebral damage. Only a few of these were seen in Cincinnati; the majority came from different parts of the United States and a few also from England, Holland, and Czechoslovakia. The serologic results on the children and with few exceptions also on their mothers were

correlated with the clinical histories and roentgenograms of the skull which were kindly supplied by a large number of interested pediatricians. Since the experience of one of us (A. B. S.) in previous years had indicated that in the absence of both chorioretinitis and cerebral calcification, the tests for toxoplasma antibodies (by the rabbit method) were almost invariably negative among children with hydrocephalus, microcephaly, convulsions, or other signs of cerebral damage of congenital or neonatal origin, not many of these were included in the present study. However, among the sixty children in the present investigation there were seventeen without chorioretinopathy, and all of them gave negative serologic tests although some of their mothers gave positive results with titers such as might be encountered in the normal population of similar age. The toxoplasma antibody titers on the children with chorioretinopathy observed during life, post mortem, or both, and in most instances also on their mothers, are presented in Table I. In three cases of pathologically proved congenital toxoplasmosis with chorioretinitis and cerebral calcification, only the mothers' sera were tested and these yielded the high dye test and complement-fixing titers encountered in experimentally infected animals. In addition to the three fatal cases just mentioned, there were two additional pathologically proved cases of infantile toxoplasmosis which helped to establish the fact that high antibody titers were the rule in recent cases of proved toxoplasmic infection. It is evident from the titers listed in Table I that the children with chorioretinopathy and other evidence of cerebral damage clearly fell into two distinct groups—one serologically compatible with a diagnosis of congenital toxoplasmosis and the other not. During the first twenty-three months of life in the serologically positive children, the dye test titers were all in the range of 1:1,024 to 1:16,384 and all but two of the ten children had complement-fixing titers of 1:16 to 1:128. The mothers' sera were all positive in the complement fixation test and their dye test titers were also high. The same was also true in the case of the children and

TABLE I. QUANTITATIVE TOXOPLASMA ANTIBODY TESTS ON CHILDREN EXHIBITING CHORIORETINOPATHY WITH OTHER SIGNS OF CEREBRAL DAMAGE AND ON THEIR MOTHERS

GROUP	TIME AFTER BIRTH (MO.)	CHILDREN			MOTHERS		
		NO.	DYE TEST TITERS	COMPLEMENT- FIXING TITERS	NO.	DYE TEST TITERS	COMPLEMENT- FIXING TITERS
Serologically compatible with con- genital toxo- plasmosis	0-5	4	4,096, 1,024 1,024	32, 32, 128	5	1,024, 1,024 4,096, 1,024 2,048	32, 64, 32 32(16), 32
	6-23	6	4,096, 1,024 1,024, 1,024 4,096, 16,384	32, 16, 2 32, 32, 128	6	1,024, 4,096 1,024, 1,024 1,024, 256	16, 32, 4 16, 32, 4
	24-71	6	256, 1,024 128, 1,024 1,024	64, 64, 128 8, 16, 16	6	256, 256 256, 256 32, 1,024	64, 16, 64 64, 16, 64
	72-84	4	64, 64 16, 16	8, 16, 0, 2	2	128, 64	8, 32
Serologically not congeni- tal toxo- plasmosis	0-5	5	0,0,0,0,0	0,0,0,0	5	4,0,0,0,0	0,0,0
	6-23	14	Undil, 0,0,0,0,0 0,0,0,0,0,0,0,0	0,0,0,0,0,0 0,0,0,0,0,0,0	14	3,4,4,16,16,<64 64,0,0,0,0,0,0,0	8,2,2,0,0,0 0,0,0,0,0,0
	67	1	0	0	1	0	0

mothers tested between 24 and 71 months after birth, although some of the antibody titers tended to be lower. Among the four children aged 6, 6½, 7 and 7 years the dye test titers were 64, 64, 16, and 16, respectively, and the complement-fixing titers were 8, 16, 0, and 2, respectively. The sera of the mothers of the 6- and 6½-year-old children were both positive with dye test titers of 128 and 64 and complement fixation titers of 1:8 and 1:32, respectively. One of the 7-year-old children had been observed by one of us (A. B. S.) since 6 months of age and his mother's serum taken at that time was strongly positive by the rabbit test.¹ It is apparent, however, that the antibody titers drop with the passage of the years, and after 6 to 7 years of age it may be difficult to establish the diagnosis of congenital toxoplasmosis in the individual case. In the serologically negative group of twenty children, nineteen were under 2 years of age and all but one gave completely negative results. The mother of the one 12-month-old child, whose serum yielded a positive dye test only in the undiluted state, had a serum dye test titer of 1:64, and it is possible that this may represent an unusually long persistence in very low titer of placentally transmitted maternal antibody.¹⁶ The occurrence of "dye-test" antibody in low titer among 40 per cent and complement-fixing antibody of low titer among 15 per cent of the mothers of this group of serologically negative children corresponds to what one may expect to find in the "normal" population of the same age, and is in sharp contrast to the results in the mothers of the serologically positive children, particularly during the first two years after birth. The whole serologic pattern is so strikingly different in the two groups, that now there appears to be no justification for considering the diagnosis of toxoplasmosis in the absence of conclusive serologic data. The assumption that the neutralizing or dye test antibodies may disappear quickly in some individuals or that infants may be slow in developing their own upon losing the placentally transmitted maternal antibody is without valid evidence and, therefore, untenable.

A remarkable difference in the incidence of cerebral calcification was found among the children with chorioretinopathy depending on whether or not the serologic evidence for congenital toxoplasmosis was positive or negative. The analysis of the data shown in Table II indicates that the incidence of cerebral calcification was 92 per cent in the serologically positive group as compared with 5 per cent in the serologically negative group among the children under 2 years of age. In the serologically positive group of ten children 2 to 7 years of age

TABLE II. INCIDENCE OF CEREBRAL CALCIFICATION AMONG CHILDREN EXHIBITING CHORIORETINOPATHY AND OTHER EVIDENCE OF CEREBRAL DAMAGE IN RELATION TO SEROLOGIC EVIDENCE OF CONGENITAL TOXOPLASMOSIS

SEROLOGIC EVIDENCE OF CONGENITAL TOXOPLASMOSIS	AGE GROUP (YR.)	NO.	CEREBRAL CALCIFICATION (% POSITIVE)
Positive	Under 2	13	92
	2-7	10	80
	Total	23	87
Negative	Under 2	19	5
	2-7	1	0
	Total	20	5

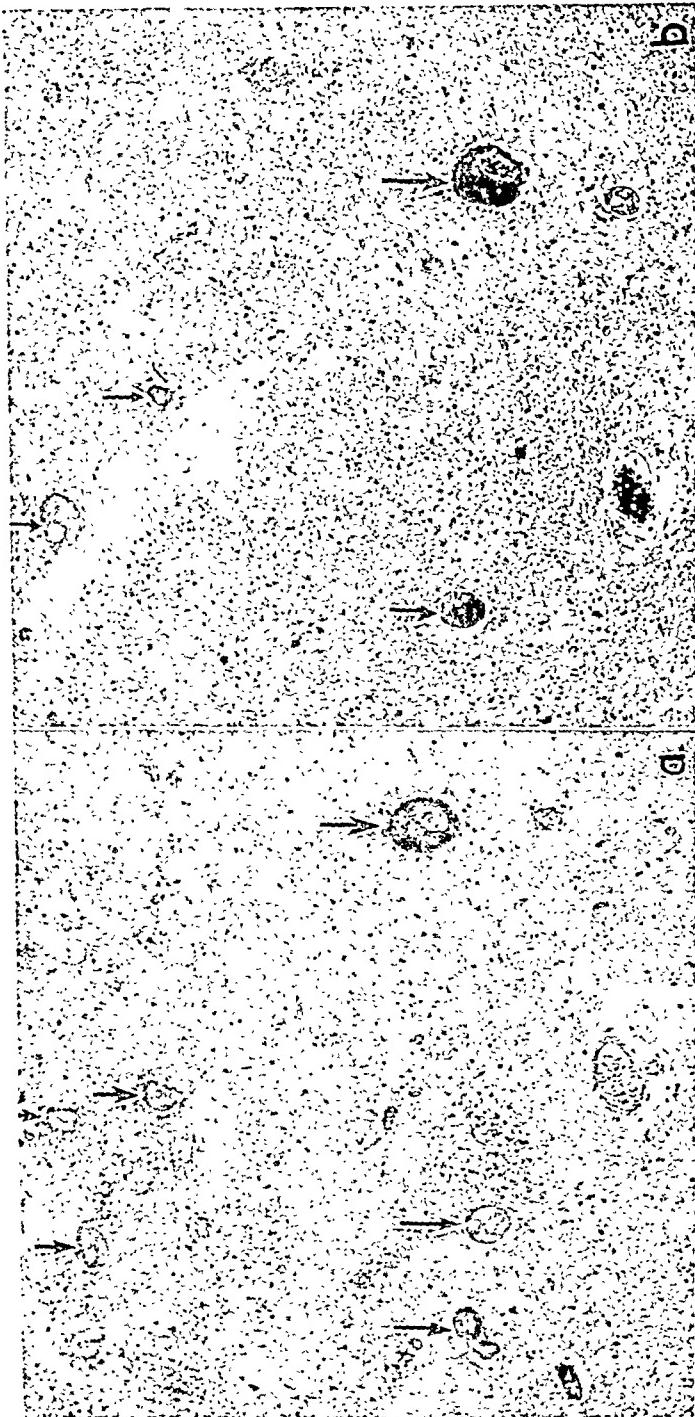


FIG. 1.—An 8-month-old infant with extensive hydrocephalus, diffuse cerebral calcification, and chorioretroinopathy, not due to toxoplasmosis. Section through cerebral cortex showing abnormal blood vessels. (a) Hematoxylin and eosin. (b) Phosphotungstic acid hematoxylin. Arrows point to affected vessels. ($\times 100$.)

at the time their sera were first tested, there were two without cerebral calcification (24 months and 44 months old); together with our colleague, radiologist Dr. Frederic N. Silverman, we had an opportunity to examine the skull roentgenograms on these two patients and could confirm the absence of grossly discernible calcification. (We are indebted to Dr. Arild E. Hansen of Galveston, Texas, and Drs. C. P. Beattie and R. S. Illingworth of Sheffield, England, for forwarding these roentgen pictures to us.) This high incidence of cerebral calcification in surviving children with positive serologic evidence of congenital toxoplasmosis is in keeping with the observations recorded in the literature on the proved fatal cases of the infantile disease; in only four of the thirty-one reported fatal, infantile cases, in which toxoplasma had been demonstrated and a search for calcification was made post mortem, was the brain found to be free of calcium deposits.

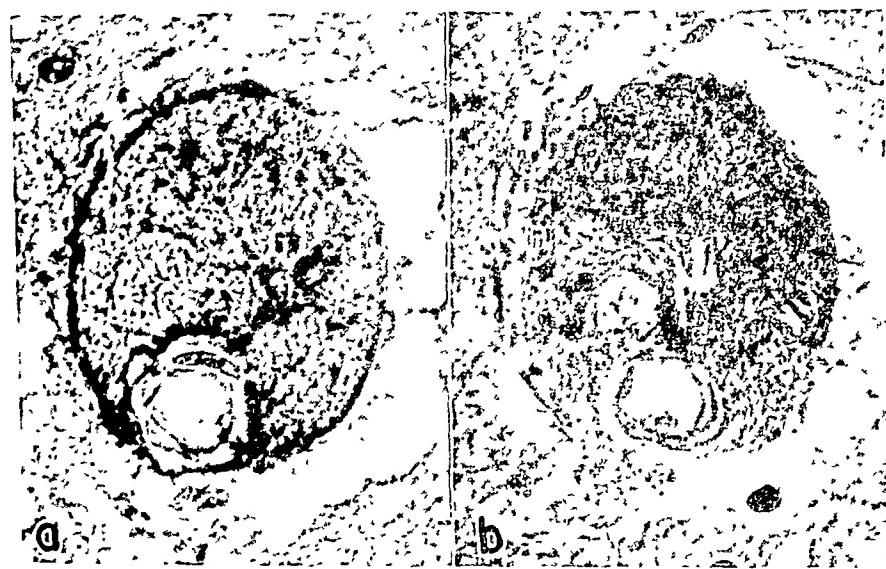


FIG. 2.—Same as Fig. 1. Abnormal blood vessel under higher magnification. (a) Hematoxylin and eosin. (b) Phosphotungstic acid hematoxylin. ($\times 810$) Figs 1 and 2 were photographed from sections supplied by Dr. W. W. Tribby of Memphis, Tenn.

In the present study only one patient was encountered who had diffuse cerebral calcification and hydrocephalus associated with the chorioretinopathy and yet gave negative serologic tests for toxoplasmosis. This patient died at 18 months of age shortly after the serologic tests had been performed and through the courtesy of Dr. Robert Ward of the Department of Pediatrics, New York University College of Medicine, we had an opportunity to examine sections of the brain, in which we could find no toxoplasma or any old, inflammatory, granulomatous lesions suggestive of toxoplasmosis. One of us (A.B.S.), however, had previously encountered two other infants (7 to 8 months of age) in whom cerebral calcification, chorioretinopathy, and internal hydrocephalus were not found, on histologic examination post-mortem, to be associated either with

toxoplasma or with an inflammatory process suggestive of toxoplasmosis. The first of these was studied through the courtesy of Drs. Gilbert J. Levy and W. W. Tribby of Memphis, Tenn. Toxoplasma antibody tests by the rabbit method (carried out by our colleague, Dr. Ruchman) were entirely negative on the mother and the child. The child died at about 8 months of age and the striking finding in the brain (in addition to the extensive internal hydrocephalus and diffuse cerebral calcification) was the many areas of softening associated with peculiar degenerative changes in many of the small blood vessels, consisting of a marked, usually eccentric thickening of the walls filled with hyaline or amorphous, granular or fibrillar, acidophilic material, staining a deep purple with phosphotungstic acid hematoxylin. (Figs. 1 and 2 were photographed from sections kindly supplied by Dr. W. W. Tribby.) The eye lesions were also noninflammatory and consisted of areas of retinal and choroid atrophy. In the second child no toxoplasma serologic tests were performed but the sections which one of us (A. B. S.) saw through the courtesy of Drs. R. V. Platou and John Dent of New Orleans, exhibited similar vascular changes in addition to cerebral calcification and chorioretinal atrophy, but neither toxoplasma nor the inflammatory lesions of toxoplasmosis could be found. It should, perhaps, be noted here that the recent report¹⁷ that diffuse torulosis in the newborn infant may give rise to cerebral calcification, hydrocephalus, and chorioretinitis needs some revision. Through the courtesy of Dr. Sidney Farber, one of us (A. B. S.) has had an opportunity to study the sections on these cases, and toxoplasma were identified as the cause of the lesions in the brain, eyes, and viscera. Tests on the sera of the mothers of two of these cases, kindly supplied by Dr. Farber, yielded the same high toxoplasma neutralizing and complement fixing antibody titers as the other mothers of children with congenital toxoplasmosis listed in Table I.

It would appear from these observations that, while chorioretinopathy in infancy and early childhood without concomitant serologic evidence of toxoplasmosis is only infrequently associated with cerebral calcification, it is not possible in the *individual* patient to be certain of the diagnosis of toxoplasmosis on any clinical grounds. All that can be said is that when chorioretinopathy is associated with cerebral calcification in infancy, the chances are approximately 90 per cent that it is due to toxoplasma. Conversely, when chorioretinopathy is encountered *without* cerebral calcification in infancy, the chances may be about 90 per cent that it is not due to toxoplasma. The precise diagnosis in the individual case can be of special importance in determining the advice that may be given to parents with regard to the expectation of normal children from subsequent pregnancies. An analysis of our own data taken together with information available on reported cases (to be published separately) of unequivocal instances of congenital toxoplasmosis, indicates that subsequent children, born at any time after the toxoplasma-infected child, are normal. This has occurred in mothers with very high titers of neutralizing and complement-fixing antibodies,¹⁴ suggesting that the persistence of these antibodies in high titer is not indicative of an active toxoplasmic infection that might be transmitted *in utero*. Since very little is as yet known about the etiologic basis of those in-

fantile cases of cerebral damage associated with chorioretinopathy which are not due to toxoplasmosis, it is highly desirable to analyze whatever information may be gathered on them.

Brief summaries of the histories and clinical manifestations available on each of the nineteen children with chorioretinopathy but without cerebral calcification or serologic evidence of toxoplasmosis are presented in Table III, and an analytic summary of the manifestations in all the children is given in Table IV. Serologic tests for syphilis were negative in all of these patients. It may be seen that microcephaly or macrohydrocephaly, convulsions, and psychomotor retardation were frequent concomitant features. In at least thirteen of the nineteen children there were no associated congenital defects, while in five, various types of congenital deformity not referable to the nervous system were present. From the available histories one cannot incriminate any clinically recognized infectious disease of the mother or exposure to roentgen rays during pregnancy. A history of prolonged or difficult labor was present in only two instances, and of premature birth in one instance among thirteen case histories with information on these subjects. Data on the status of preceding or succeeding siblings is as yet very scanty. In seven of twelve cases, the patient was the first-born child and no information is as yet available on the result of subsequent pregnancies; in four instances the preceding siblings were all well, and in another family there were three preceding normal children, one preceding child with "a questionable spell" at 2 years of age and some retardation in motor development, and one child, appearing entirely well at 6 weeks of age, born subsequent to the patient. One of the patients in this group (No. 7 in Table III; Fig. 4) died at 12 months of age of a bronchopneumonia while this report was in preparation. The brain of this patient showed evidence of defective development (multiple microgyria, one open lateral ventricle with multiple cysts in a highly proliferated choroid plexus, abnormality in convolutions and sulci) but not of any inflammatory process; grossly one eye showed evidence of retinal and choroid atrophy while the other, with microphthalmus and microcornea, exhibited a retrobulbar mass in the vitreous.

It is not at all unlikely that the syndrome of infantile chorioretinopathy and cerebral damage without cerebral calcification or serologic evidence of toxoplasmosis may ultimately be associated with a variety of etiologic factors. In the first description of the damage caused the human fetus by excessive exposure of the mother to x-rays, Aschenheim¹⁸ noted that a child with microcephaly and imbecility had chorioretinitis in both eyes which also exhibited microphthalmus and optic atrophy. In his description of the bilateral retrobulbar fibroplasia which develops in certain premature infants, Terry¹⁹ reported one case (Case 6, 7 months old) in which retrobulbar fibroplasia was present only in the right eye while the left eye presented a lesion in the macular region resembling a "healing chorioretinitis." Both Gregg²⁰ and Swann et al.²¹ in their reports on congenital cataracts in children born of mothers who had German measles early in pregnancy, mentioned an instance in monocular cataract cases in which the other eye presented chorioretinal lesions. While the possibility of toxoplasmosis

TABLE III. CHORIORETINOPATHY WITHOUT CEREBRAL CALCIFICATION OR SEROLOGIC EVIDENCE OF TOXOPLASMOSIS: DATA ON INDIVIDUAL PATIENTS

PATIENT				CHIEF MANIFESTATIONS AND PERTINENT HISTORY
No.	NAME, RACE, AND SEX	AGE AT TIME OF TEST (MO.)	STATE OR COUNTRY	
1	Br. White Male	1 $\frac{1}{4}$	Missouri	O D—posterior lenticonus, disc white, large areas of old chorioretinitis at posterior pole extending from disc laterally to involve macular area, vessels normal. O S.—posterior lenticonus, disc white, large area of old chorioretinitis just lateral to but not involving disc, macula probably involved. No "activity," masses in vitreous or fibrous bands in either eye. Head enlarged (41.4 cm.) with chest 32.2 cm. Subdural tap negative. Ventricular fluid clear, slightly yellow, no cells, protein 94 mg. per cent. Periodic, convulsive jerking of both arms and legs. Harsh, loud, systolic murmur over entire precordium. Mother in labor 15 $\frac{1}{2}$ hours. Courtesy of Drs. Bailey, Webb, John E. Byrne, and Gerald E. Hughes of St. Louis Hospital.
2	Pr White Male	1 $\frac{1}{2}$	Louisiana	Retinal degeneration and optic atrophy O. U. Progressive since birth with bilateral convulsions. Courtesy of Dr. T. E. D. Beaman of Chester City Hospital. (See Fig. 3.)
3	Mo. White Female	2 $\frac{1}{2}$	England (Chester)	Bilateral microphthalmus with extensive choroidal degeneration. Convulsions since birth, twitching of arms and legs accompanied by rigidity and some opisthotonus, every 15 minutes. CSF: no cells, 80 mg. per cent protein. Bilateral talipes equinovarus. Full term breech delivery. Mother treated for hemorrage and hydranmios during pregnancy but no history of infection or exposure to x-ray. No history of convulsions on either side of family. Patient is first born child. Courtesy of Dr. T. E. D. Beaman of Chester City Hospital. (See Fig. 3.)
4	Ba White Female	4	Arkansas	Blind, bilateral chorioretinitis affecting macula. Convulsions and retarded development. No history of maternal illness during pregnancy. Courtesy of Dr. Wm. A. Reilly, University of Arkansas School of Medicine, Little Rock.
5	La. White Female	5	Ohio	Many areas of depigmentation and chorioretinitis degeneration in both eyes, more diffuse in left than right; discs and vessels normal; pupils equal and react to light and accommodation. Convulsive seizures several times daily began during third month and continued with increasing frequency. Cortical atrophy present. CSF: normal with 33 mg. per cent protein. Electroencephalogram showed diffuse, slow dysrhythmia believed to be due to organic brain disease. (Can hold up head but unable to sit up and coordination of hands and feet not evident.) Spontaneous, full term delivery after 1 $\frac{1}{2}$ hours of labor. Courtesy of Drs. G. William Sunderman and Alexander T. Bunts of Cleveland Clinic.
6	Tr. White	6	Holland	Poor vision, bilateral choroiditis. Microcephaly. Deformity of right ear and "skin . . . covered with little papulae." Born two weeks before expected date after short labor. Cyanotic during first 48 hours of life. Mother suffered from hyperemesis during pregnancy but no illness was recognized. Family history and diet during pregnancy "not abnormal." Patient is first born child. Courtesy of Prof. S. van Creveld of Amsterdam.

TABLE III—CONT'D

PATIENT				(CHIEF MANIFESTATIONS AND PERTINENT HISTORY)
NO	NAME, RACE, AND SEX	AGE AT TIME OF TEST (MO.)	STATI ON OR COUNTRY	
7	Lo White Female	7	Ohio	O D—microcornea, fixed pupil, and microphthalmus O S—"large area of retinal degeneration surrounded by excessive pigment giving appearance of old, healed retinitis." Repeated convulsions since birth with almost no psychomotor development Microcephaly Cleft palate, multiple hemivertebrae, pigeon breasted Born at term following prolonged traumatic delivery Seven preceding siblings all well See Fig 4 Patient studied at Children's Hospital, Cincinnati
8	Fo White Female	7	England (Shef field)	Fundi showed pale areas varying in size from a twelfth to a half disc diameter with surrounding black pigment Three such areas in right and seven in left Questionable microcephaly Poor psycho motor development CSF normal First born child from a normal, full term delivery Mother well during pregnancy, x-rayed once for diagnosis Courtesy of Professors R S Illingworth and C P Beattie of the University of Sheffield
9	Jo White Male	8	Utah	O S—dumbbell shaped area of an old scarred chorio retinitis, lower portion whitish yellow, upper portion dark red with flecks of black pigment in it, macula normal O D—normal Pneumoencephalogram showed moderate dilatation of both lateral ventricles with evidence of some cerebral agenesis Electroencephalogram considered abnormal because of good deal of three per second activity CSF was normal Transitory febrile illness with convulsions and seeming blindness at 7½ months of age Vision reappeared and apparently normal motor and psychic development was noted at 15 and 16 months of age First born child, delivered by elective Cesarean section No maternal illness or exposure to x-ray during pregnancy Courtesy of Dr John A Anderson, University of Utah, Salt Lake City
10	Bu White Male	10	Calif format	O S—one large area of old chorioretinitis in region of macula O D—normal Microcephaly, psychomotor retardation, unable to hold up head or sit alone Born two weeks prematurely after prolonged and difficult labor No maternal illness or exposure to x-ray during pregnancy First born child Courtesy of Dr John H Doval, Sacramento, Calif
11	Hi Negro Male	11	Louisiana	"areas of suggestive chorioretinitis" in both eyes Microcephaly, dilated lateral ventricles, and cerebral agenesis, occasional muscular twitchings, cannot crawl or sit alone First born child, with uncomplicated delivery after eight months' gestation Courtesy of Dr R V Platou, Tulane University, New Orleans
12	Ma White Male	11	Ohio	Poor vision, retinal degeneration suggested by peppery appearance of fundi, both optic discs gravish Left internal strabismus Microcephaly with cerebral atrophy CSF normal Does not crawl, sit, or vocalize Pigeon breasted, phimosis No maternal illness or exposure to x-ray during pregnancy Spontaneous delivery Two preceding siblings normal Patient studied at Children's Hospital, Cincinnati

TABLE III.—CONT'D

PATIENT				CHIEF MANIFESTATIONS AND PERTINENT HISTORY
NO.	NAME, RACE, AND SEX	AGE AT TIME OF TEST (MO.)	STATE OR COUNTRY	
13	St. Negro Female	12	Maryland	O.D.—large atrophic lesion with pigmented margins at temporal side of macula and a similar, smaller lesion but three times the size of the disc in the upper temporal region. O.S.—large atrophic lesion, "many times" the size of the disc in the temporal area but sparing the macula. Vessels, media, and discs normal. Spastic, retarded infant with major generalized convulsions since 11 months of age. No maternal illness or exposure to x-rays during pregnancy. Courtesy of Dr. J. Neill Lysaught, Harriet Lane Home, Johns Hopkins Hospital.
14	Ro. Negro Male	13	Louisiana	Area of chorioretinitis involving macular region of right eye, variable right internal strabismus. Microcephaly since birth, spastic, retarded, mongoloid facial features, mannerisms of mentally deficient infant. Patient is fifth child, from a normal, full-term delivery. Preceding siblings normal except one with questionable "spells" at 2 years of age and delay in walking until 2 years of age; one succeeding sibling normal at 6 weeks of age. No maternal illness during pregnancy and no family history of retarded development. Courtesy of Dr. R. V. Platou, Tulane University, New Orleans.
15	Br. White Female	13	Holland	Bilateral chorioretinitis. Hydrocephalus since 1 month of age without preceding infection or trauma. CSF: xanthochromic, no cells, "contains albumin." Normal, spontaneous delivery. No maternal illness or exposure to x-rays during pregnancy. Courtesy of Prof. S. van Creveld of Amsterdam.
16	Fr. White Male	14	England (Shef- field)	O.S.—fundus shows large white areas mostly circular with large amounts of black pigment at periphery or within the affected areas. O.D.—removed at 6 months of age because of "tumor mass" which unfortunately was lost before histologic examination. Microcephaly. CSF was normal. Smiled at 2 months, sat up at 6 months, and can stand and walk with support at 13 months. First born child from a normal, full-term delivery. No maternal illness during pregnancy; single exposure to x-rays for diagnostic purposes between seventh and eighth month of pregnancy. Courtesy of Professors R. S. Illingworth and C. P. Beattie of the University of Sheffield.
17	Ol. White Male	15	Michigan	Bilateral retinal atrophy simulating old chorioretinitis. Convulsive episodes since 2 months of age; occasional unexplained febrile episodes. No maternal illness during pregnancy. One preceding 4-year-old sibling normal. Courtesy of Dr. J. C. Montgomery of Detroit.

TABLE III.—CONT'D

PATIENT				CHIEF MANIFESTATIONS AND PERTINENT HISTORY
NO.	NAME, RACE, AND SEX	AGE AT TIME OF TEST (MO.)	STATE OR COUNTRY	
18	Bo. White Female	18	New Jersey	Blindness first noted at 3 months of age; bilateral microphthalmus and chorioretinitis. Convulsions without fever at 5 months and at 14 months. Could sit alone at 10 months, stand with support at 12 months, and spoke a few words at 18 months. Born during sixth month of pregnancy after sudden, spontaneous, severe maternal hemorrhage; birth weight 2 pounds, 4 ounces, but weighed 12 pounds at 3 months. No maternal illness or exposure to x-rays during pregnancy and no history of familial disease. One preceding, 4-year-old sibling entirely normal. Courtesy of Drs. C. P. Defuccio and R. G. Berggreen, Medical Center, Jersey City.
19	Bu. Female	67	Louisiana	Unusually severe, long standing, healed choroiditis. Convulsions and mental retardation. Head normal size. No maternal illness or exposure to x-rays during pregnancy. Courtesy of Dr. R. D. Johnson, Ochsner Clinic, New Orleans.

TABLE IV. CHORIORETINOPATHY WITHOUT CEREBRAL CALCIFICATION IN INFANCY NOT DUE TO CONGENITAL TOXOPLASMOSIS; CLINICAL MANIFESTATIONS AND HISTORY IN A GROUP OF NINETEEN CHILDREN

<i>Age</i> (at time of study)	
Under 12 months	12
12 to 18 months	6
67 months	1
<i>Eyes</i>	
Fundi. Atrophic or degenerated areas without pigment but surrounded by zones of increased pigmentation, frequently described as "old, healed chorioretinitis," situated in various parts of the fundus and often affecting the macula.	
Both eyes, 14; one eye only, 4; not stated, 1.	
Blind	4
Micropthalmos	4
<i>Brain</i>	
Microcephaly	8
Macrohydrocephaly	4
Convulsions	11 (since birth or first appearance at 2, 3, 5, 7, or 11 months of age).
Psychomotor retardation	10 definite; 3 slight or questionable; others unknown.
Cerebrospinal Fluid	In 3 of 8 studied protein increased up to 90 mg. per cent.
<i>Other Congenital Defects</i>	
Definite	5
Questionable	1
None	13
1. Cleft palate; multiple hemivertebrae	
2. Deformed right ear	
3. Talipes equino-varus, bilateral	
4. Mongoloid features in Negro child	
5. Pigeonbreasted	
Cardiac type?	
<i>History of Siblings</i>	
Of 12 families studied, patient first born in 7; preceding children in other 5 families all normal, and 1 succeeding child also normal.	
<i>History of Mothers During Pregnancy</i>	
Infectious Disease	0/15
Exposure to X-Ray	None in 11 and single exposures for diagnosis in 2 of 13 studied.
Prolonged or difficult labor	2/13
Premature birth	Only 1 of 13 definite; at 6 months associated with hemorrhage.

cannot be eliminated in these cases, these observations, nevertheless, suggest that a variety of factors may prove to be responsible for nontoxoplasmic chorioretinopathy in infancy.



Fig. 3.—Patient No. 3, Table III. Photograph reproduced through courtesy of Dr. T. E. D. Beavan of Chester, England.



Fig. 4.—Patient No. 7, Table III. Photographed at 12 months of age, shortly before death.

SUMMARY

The new, quantitative, *in vitro*, toxoplasma dye and complement fixation tests give a certainty to the diagnosis of congenital toxoplasmosis that was not possible hitherto. By means of these tests it was found that chorioretinopathy associated with other evidence of ocular and cerebral damage or defects and not due to toxoplasmosis, is not infrequently encountered in infancy and early childhood. When infantile chorioretinopathy was associated with *positive*, quantitatively significant serologic tests for toxoplasmosis, the incidence of grossly perceptible cerebral calcification in roentgenograms of the skull was approximately 90 per cent of 23 cases, while in a group of twenty children with chorioretinopathy and *negative* serologic tests for toxoplasmosis the incidence of cerebral calcification was only 5 per cent. Although the syndrome of infantile chorioretinopathy, without associated cerebral calcification or evidence of toxoplasmic infection will probably prove to have a multiple etiology the available data suggest defective development rather than destructive, necrotic lesions as the more probable pathologic basis. Attention is also called to the existence in infancy of a syndrome characterized by extensive destruction of brain tissue with hydrocephalus, diffuse cerebral calcification, and chorioretinopathy, associated with bizarre, "degenerative" changes in the small blood vessels which can be distinguished from that of congenital toxoplasmosis only by serologic tests or pathologic examination. The serologic elucidation of the diagnosis, in the individual case, is of particular importance with regard to the outlook for subsequent children, since the accumulated data indicate that normal subsequent children have been born in all instances in which the diagnosis of congenital toxoplasmosis could be made with certainty either on pathologic or quantitative serologic grounds.

REFERENCES

1. Sabin, A. B.: Proc. Soc. Exper. Biol. & Med. 51: 6, 1942; Advances in Pediatrics 1: 1, 1942.
2. Cowen, D., Wolf, A., and Paige, B. H.: Arch. Neurol. & Psychiat. 48: 689, 1942.
3. Heidelman, J. M.: Arch. Ophthalmol. 34: 28, 1945.
4. Johnson, L. V.: Arch. Ophthalmol. 36: 677, 1946.
5. Ruchman, I.: J. Lab. & Clin. Med. 33: 87, 1948.
6. Gard, S., as reported by Magnusson, J. H., and Wahlgren, F.: Acta Pathologica 25: 215, 1948.
7. Jacoby, N. M., and Sagorin, L.: Lancet 2: 926, 1948.
8. Lelong, M., et al.: Arch. Frane. de Pediat. 5: 113, 1948.
9. Winsser, J.: Ann. Paediatrici 171: 219, 1948.
10. Binkhorst, C. D.: Toxoplasmosis: A Clinical, Serological, and Histopathological Study With Special Reference to the Eye Manifestations, 1948 (Stenfert Kroese, Leiden).
11. DeToni, G.: Minerva Medica 39: 157, 1948.
12. Tolentino, P., and Buelossi, A.: Polyclinico Infantile, 1948 (N. 6).
13. Sabin, A. B., and Ruchman, I.: Proc. Soc. Exper. Biol. & Med. 51: 1, 1942.
14. Warren, J., and Russ, S. B.: Soc. Exper. Biol. & Med. 67: 85, 1948.
15. Frenkel, J. K.: Proc. Soc. Exper. Biol. & Med. 68: 634, 1948.
16. Feldman, H. A., and Sabin, A. B.: In press.
17. Sabin, A. B., and Feldman, H. A.: Science 108: 660, 1948.
18. Aschenheim, E.: Arch. f. Kinderh. 68: 131, 1921.
19. Terry, T. L.: Arch. Ophthalmol. 29: 36, 1943.
20. Gregg, N. M.: Transact. Ophthalmol. Soc. Australia (BMA) 3: 35, 1941.
21. Swann, C., Tostevin, A. L., Moore, B., Mayo, H., and Black, G. H. B.: Med. J. Australia 2: 201, 1943.

THE DEVELOPMENTAL ASPECT OF CHILD VISION

ARNOLD GESELL, M.D.
NEW HAVEN, CONN.

THE development of vision in infancy and childhood is very complex, for the simple reason that it took countless ages of evolution to bring human vision to its present advanced state. Visual perception ranks with speech as a distinctive human trait and it passes through comparable growth stages. Moreover, vision is not a separate, isolated function; it is profoundly integrated with the total action system of the child—his posture, his manual skills and motor sets, intelligence, and even personality make-up. Indeed, vision is so intimately identified with the whole child that we cannot understand its economy or its hygiene without investigating the whole child.

Under a program of cooperative research at the Yale Clinic of Child Development, we have made periodic studies of the normal visual functions in their relation to the total action system of the child at a score of advancing age levels from early infancy to the tenth year.* In general, about fifty children were investigated at each age. The data were gathered through clinical examinations of behavior patterns; naturalistic observations of spontaneous behavior at home, school, and guidance nursery; graded tests of visual skills; optometric measurements; and retinoseopic determinations of the brightness, the motion, the direction, speed, and color of the retinal reflex in the natural reactive eye. All the findings were analyzed and compared from age to age and from child to child to define growth trends.

THE EMBRYOLOGY OF VISUAL BEHAVIOR

Studies of viable premature infants yielded data concerning the fetal stages of visual development. This development is very precocious. Vision has a motor basis. The eyes of the fetus move beneath their fused lids as early as the twelfth week after conception. For over six months prior to birth the eyes, although in darkness, move with increasing coordination to meet the demands that will be made upon them when subjected to light. Two months before birth the retina assumes an adult arrangement. Four lunar months before birth the fovea forms and establishes itself definitively at the final adult distance from the optic nerve head. This remarkable fact certifies to the profound importance of vision in the organization of human behavior. The eye itself will more than double its weight before birth. The brain will increase three and one-half times from birth to maturity, and the body twenty-one times. Nevertheless, the distance between fovea and nerve head remains an absolute, a fixed pivotal area in all the ensuing morphogenesis of the action system.

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*The results of this investigation are reported in a volume now in press, Gesell A., Ilg F., and Bullis, G. E. (assisted by V. Ilg and G. N. Getman). *Vision: Its Development in Infant and Child*, New York, 1949, P. B. Hoeber, Inc., Medical Book Department of Harper & Brothers. The investigation received generous support from the Bureau of Visual Science of American Optical Company.

A healthy fetal-infant, born about eight weeks prematurely, exhibits two behavior patterns highly significant in the development of vision. He assumes a tonic-neck-reflex posture with the head averted to one side, the arm at that side extended, the opposite arm flexed at the shoulder, simulating a fencing attitude. His early ocular fixations will be channelized in the direction of this attitude. He does not give true regard to a dangling four-inch ring slowly moved across the field of vision; but the eyes move saccadically in momentary after-pursuit.

The visual competence of the full-term newborn infant exceeds that of the premature, indicating that intrinsic maturation is more basic than experience in the patterning of visual behavior. Incipient fixation of a near, approaching object is observable in the first day of life; sustained fixation of a near object occurs in the first week; fixation of more distant objects occurs at the end of the first month. When the neonate fixates an object of interest, his sporadic bodily activities tend to subside. The fixational response clearly involves the entire action system to some degree. The scope and complexity of his vision are delimited by the postural attitudes of eyes, head, body, limbs. With increasing maturity the visual system assumes more autonomy, but it never operates altogether independently of the total action system.

The eyes, however, take the lead in the conquest and manipulation of space. The baby takes hold of the physical world ocularly long before he grasps it manually. He can pick up a pellet (7 mm. in diameter) with his eyes full twenty weeks before he picks it up with his fingers.

Although an infant stares vaguely into faraway space, his structured visual world begins in the near vicinity of his eyes. For him the space-world is not a fixed, static absolute. It is a plastic domain which he manipulates in terms of the nascent powers of his growing action system. The supine infant, the runabout infant, the sedentary school child, each has his own space-world with a distinctive set of planes of regard. Biological space is a function of the organism. The space-world of the myope differs from that of the hyperope. Every child organizes his space-world in obedience to laws of development, general for the species and unique for himself.

FUNCTIONAL COMPLEX OF THE VISUAL SYSTEM

This organizational process operates in three basic functional fields: skeletal, visceral, and cortical. These fields are correlated with the three primary embryological divisions and with the conventional fixation-focus-fusion triad. The *skeletal* component of this functional complex seeks and holds a visual image (optical stimulus); the *visceral* component discriminates and defines the image; the *cortical* unifies and interprets it.

The three functional fields develop conjointly but by no means uniformly. The ratio between skeletal, visceral, and cortical manifestations varies with advancing stages of maturity. In the course of individual development, gradients of performance are built up concurrently but unevenly in the three basic functional fields. Four factors enter into these gradients: (1) coordination, which refers to the teaming of the eyes and right versus left dominances; (2)

reach, which refers to the distance and precedence of the planes of regard; (3) *scope*, which concerns the important relationships between central and peripheral vision; (4) *drift*, which denotes the growth trends signified by the break and recovery span of ocular ductions, the preferred zones of regard, and accommodation and dominant directionalities.

All these variables and gradients are subject to the organizing processes of growth. Accordingly, each age of infancy and childhood affords a distinctive constellation of visual behavior patterns. With so many components and variants entering into the functional complex of the visual system, it is natural that no two children should see exactly alike. The possible constellations of visual components, normal, atypical, and abnormal, are beyond enumeration. The individual variations, however, are governed by a general ground plan of ontogenetic development. This ground plan is manifested in five distinguishable areas: eye-hand coordination, postural orientation, fixation, projection, and retinal response. Our studies, although preliminary, have demonstrated that it is possible to formulate developmental gradients in each of these areas.

The adequacy of child vision cannot be appraised by a simple refractive criterion of acuity. All vision is mediated by an intricate functional complex. The task is to interpret vision in terms of over-all achievement and to analyze that achievement in terms of the developmental status of the organism.

The retinoscope has revealed an intimate relationship between the functional complex of the visual system and the maturity of the total action system. The retinoscope projects a beam of light upon the reflecting surface of the retina. The examiner takes note of the returning light and finds that it varies significantly in relation to identifiable moments of the visual act. A comparison of the retinal reflex patterns at near and far shows that the infant is more fully organized for vision in the near point areas than at distance. An increase of brightness in the reflex occurs characteristically at the moment when the infant identifies a target. At that moment the eye and the brain appropriate the object of interest. Coincidentally, the reflex registers an *against* motion which, by streak retinoscope, indicates a *minus* refractive value but not necessarily a fixed myopic deviation. For this minus may increase or decrease with the stress of the task and at certain moments of adjustment may give way to a *with* motion which suggests a shift in the hyperopic or *plus* direction. Such variations seem paradoxical, but if one thinks of the reaching eye as essentially a teleceptive prehensory organ, these patterns of response are understandable. The visual system gropes and grasps and manipulates. The infant manipulates toys, the preschool child models clay, the school child copes with the symbolic targets of a printed page; but the retinocortical manifestations for all three types of manipulation are comparable.

The retinoscopic and associated findings indicate that the visual mechanism of the growing child is in a labile condition, dynamically and developmentally. Superimposed upon a basic delimiting refractive state is a margin of adaptability which is manifested in the brightness, motion, direction, color, and velocity of the retinal reflex. Such a relationship between consolidated and plastic structure would seem to be a necessary condition of growth.

DEVELOPMENTAL MANIFESTATIONS

We need broadened methods of observation of the young eye in action and also of the underlying growth factors. The concept of development adds a new dimension to all problems of visual care, to diagnosis, supervision, prevention, education, training, and re-education. This concept applies with equal force to the normal and to the visually disadvantaged child. With failure to recognize developmental mechanisms, the culture tends to make excessive visual demands on the young child in the form of premature reading and writing tasks.

Both ophthalmology and optometry stem historically from the study of the mature adult eye. Many of the prevailing principles and procedures naturally reflect this adult orientation. It is increasingly evident that such an orientation introduces certain errors and shortcomings. We are confronted with the sobering realization that the child is never a miniature adult, even in his visual equipment. He is qualitatively a different organism and he is always changing qualitatively at a more rapid rate than the adult. This is peculiarly true of his visual system.

It should not be necessary to wait until belated adolescent and adult years to determine the efficiency of his visual functions. With increased knowledge the developmental status of these functions can be appraised and supervised throughout the period of infancy and childhood. In this sense the developmental aspect of child vision has implications for preventive and supervisory pediatrics.

Even on the basis of present information, it is possible to distinguish visual behavior traits which are characteristic of certain maturity levels. We may illustrate this by considering various deviations of visual behavior which appear at three different age periods, namely: infancy, the preschool years, and the school years.

INFANCY

Infants reveal their visual individualities in ocular and other postural attitudes and demeanors. Virtually all infants repeatedly assume, in one form or another, the tonic-neck-reflex posture and the symmetro-tonic-reflex posture during the first half-year of life. These postures, both quiescent and active, constitute a morphogenetic matrix for the basic patterning of the coordinations, dominances, and functional correlations of eyes and hands, singly and in pairs.

Excessive hand regard, if not due to retarded development, may signify a myopic trend. Excess manifests itself in the intensity and duration of episodes and in a marked continuation beyond the age of 12 weeks. One of our myopic subjects, now 6 years old, held the hand regard attitude so persistently and steadily in infancy that he acquired the nickname "Statue of Liberty." Delayed hand regard is a symptom of retardation, but it may also be associated with normal intelligence and atypical spatial manipulation.

Another deviation consists in a poorly defined postural orientation, a neutral tendency to assume somewhat indifferently either a right or a left tonic-neck-reflex. Ordinarily, there is a defined preference for right or left which must have correlations with ocular and manual dominance, and with the organization

of the functional asymmetry of the total action system. Little is known about the nature of these correlations, but we may be sure that they have predictive import for later visual patterns. The whole subject needs extensive investigation, because it has significance for preventive hygiene.

Complicating clinical factors, however, must not be overlooked. Minimal cerebral injuries are more common than is ordinarily supposed, and they account for certain persisting as well as temporary visual deficits. In some instances there are associated personality deviations occasioned by the visual defect or traceable to a damage of the cortical mechanisms concerned with emotional organization.

Strabismus is a common symptom of minimal injury. It frequently undergoes spontaneous resolution. It may also be combined with oculomotor incoordination and atypical eye-hand patterns in which arms and fingers assume eccentric postures. This leads to bizarre patterns of exploitative behavior. The infant, for example, may poke and twiddle a cube in a restricted, perseverating manner. Atypical motor patterns may persist for three years or more. These mild neurological difficulties may set up an extremely complicated interaction of developmental potentialities and dynamic forces. The mild motor disabilities may be associated with speech defects, with imperfect manual dominance, and with delayed integration. Such syndromes lie at the basis of certain school entrance problems and cases of reading disability. Vision is involved, but the total behavior equipment of the child demands searching individual study. For these reasons, eye specialists and educators must reckon with the clinical category of minimal cerebral injury, and must be alert to its developmental manifestations. The early symptoms of minimal cerebral injury are often overlooked. They do not yield to the ordinary methods of clinical neurology, but they can be elicited by a systematic developmental examination of infant behavior patterns.

PRESCHOOL YEARS

Visual difficulties come to somewhat franker expression in the preschool years. The child begins to leave the confines of the home and is thereby brought into more frequent comparison with his peers. If he has serious ineptitudes, he reveals them in his play activities, in postural demeanors, in his adjustments to a nursery school group, in his use of cup and spoon, of crayon and paints, and in his response to picture books. He may show a moderate amount of staring (or perhaps too little). He may show forms of caution, fear, and withdrawal which may denote visual, rather than purely emotional, factors. Indeed, even his atypical personal-social relations with his companions may have a visual basis in faulty space manipulation.

On the basis of everyday patterns, a discerning teacher may detect evidences, more or less predictive, of potential reading disabilities—specific weaknesses in drawing and in form perception; ill-defined handedness; reduced acuity; atypical directionalities in movement patterns, and so on. When the norms of visual behavior are more widely known by parents and teachers, it will be possible to use naturalistic observations of spontaneous behavior for the benefit of children who need early guidance in solving their visual problems. Such observations should both precede and supplement formal visual skill tests. They become

doubly important, under professional guidance, for appraising the responses of the child to lens assistance and to special visual training procedures. Naturalistic observation of the spontaneous child is at times more valuable than technical observation, because it brings into view the total child and his unitary action system.

In considering the visual economy of a young child, one does not think only in terms of refraction and fusion. One considers the over-all organization of his visual equipment, and asks whether he has the ability to meet the normal visual tasks demanded by the culture. A developmental approach to his problem puts us in a better position to give him the developmental support which will benefit him more than a full refractive correction would. Indeed, in some instances, a full correction given too early and insisted upon too long may create a crutch which, in turn, becomes an impediment. The growing visual equipment then organizes about the full-strength lens, whereas a more natural and advantageous organization could have taken place with the aid of lenses of lesser strength, carefully timed to put the organism on its own best resources. The same principle applies to training procedures and to the planning of eye-care regimes. Wise timing in small, well-spaced sessions, with interested motivation, is more efficacious than an overstrenuous practice-makes-perfect program. In all programs of visual care it is important to appraise the kind and degree of acceptance manifested by the child.

The causative factors underlying strabismus are so diversified that generalized discussion is almost impossible. There are two major types of strabismus, one predominantly visceral, the other predominantly skeletal. Symptoms and premonitions are prone to occur during transitional stages of readjustment in equilibrium—for example, at 21 to 24 months. At these stages, the organism is more loosely organized in order to give play to counterpoised opposites. The looseness or morphogenetic flux characterizes the action system as a whole and more or less evenly paired body members and paired functions, such as flexors versus extensors, abduction versus adduction, and so on. Accordingly, a liability to strabismus may declare itself in frank eye discoordination or, more indirectly, in faulty motor demeanors and awkwardness. A clumsy hand, a foot drag, or a postural slump on the "weak side" may come into evidence in a 2½-year-old child as a precursor of a manifest strabismus a year or two later. Such a presquinter, if accurately identified, on developmental premises would be approached orthopedically first, and orthoptically later, with due consideration as to whether the condition is primarily skeletal or visceral in character.

SCHOOL YEARS

The culture is not too aware of the school beginner's difficulties and potentialities. Rightly construed, many of his difficulties are actually symptoms of potentialities—new abilities in the making. Lacking finesse, it deals with him en masse, and tends to use rigid and undiscriminating procedures. If he is unfortunate enough to enter a strictly regimented school, his teacher frowns upon him even if he drops a pencil. Now, he is very likely to drop a pencil, because his patterns of visual behavior are not adequate to all the demands which are made upon his seeing and interpreting equipment.

All too soon, he encounters difficulties which are due to the discrepancy of the culture and his own immature visual and manual structures. He may have trouble in adapting to the blackboard, and in making adjustments from far to near and near to far. The culture, as embodied by the schoolroom, may make unreasonable demands upon sustained attention at a stage of development when he is geared to brief and multiple adjustments that require a shifting, flexible activity program. If he began to identify letters and numerals at the age of 2½ years, he is not likely to experience undue difficulty in responding to reading instruction, whatever method may be used. However, many children are in a phase of development, or they present individual maturity traits which make it difficult or impossible for them to profit from the prevailing method of instruction. A sizeable fraction of these children in a year or two are classified as poor readers, nonreaders, and slow readers. Broadly speaking, the difficulties of these academically disadvantaged children are due to a rather clumsy disparity between the educational environment of the school and the organisms which are in attendance.

All children, after the age of 5 years, undergo fundamental and more or less striking reorganizations in their visual equipment. They acquire new abilities, but not always in balanced or well-timed relationships. Often new trends become observable by the age of 5½ years. Appraisal at 6 years may show a developmental direction in the nature of the interaction of the visceral and skeletal functions. At 7 years, there may be frank evidence of such directional trends. Typically the visceral-skeletal linkage is relatively tight at the age of 7 years. By 8 years, this tightness gives way to a looser and more facile interplay. By 9 years, the looseness is being superseded, in turn, by a more robust consolidation of the visceral-skeletal components.

It is difficult, with our present meager knowledge, and on the basis of a single visual appraisal at 5 years, to predict the probable course of development in the years from 5 to 10; but systematic examination and supervision of the visual functions in the preschool years will serve to identify children who present potential difficulties in book learning and other school tasks.

This possibility, however, should not blind us to the fact that the culture is making unreasonable demands upon many young children. The demands overburden the limited powers of spatial manipulation and, in many instances, rearrangement and amelioration of the cultural demands would be a more basic solution than a therapeutic approach to the visual handicap. In a flexible educational system, both lines of approach may be conjointly utilized; the one directed toward the environment, the other toward the organism.

The pediatrician, therefore, may well have an interest in the developmental aspect of child vision. He is in a position to recognize behavior patterns which are symptomatic of visual difficulties and which may be serious enough to require specific guidance or referral to a specialist.

Child care involves eye care, and eye care involves child care. Developmental optics in theory and in application is concerned with the development and organization of visual functions in their dynamic relation to the total action system.

REVASCULARIZATION OF THE BRAIN THROUGH ESTABLISHMENT OF A CERVICAL ARTERIOVENOUS FISTULA

EFFECTS IN CHILDREN WITH MENTAL RETARDATION AND CONVULSIVE DISORDERS

CLAUDE S. BECK, M.D., CHARLES F. MCKHANN, M.D., AND
W. DEAN BELNAP, M.D.
CLEVELAND, OHIO

MENTAL retardation, convulsive disorders, and sensory-motor impairment are among the most common of pediatric problems. The gliosis characteristic of these conditions has been found to interfere with blood supply to cerebral tissue.

We have attempted correction of the deficiency in circulation by production of an anastomosis between the common carotid artery and the internal jugular vein, resulting in a redistribution and increase of blood flow to the brain. This can be performed with reasonable safety to the patient. Results given herein indicate that re-establishment of blood supply to parts of the brain by arteriolization of the venous system is a rational surgical procedure. Production of an arteriovenous fistula for therapeutic purposes has been performed experimentally in animals, and arteriolization of the venous system has been found to be of benefit in vascular diseases of human extremities. We believe, however, that this report is the first dealing with the therapeutic benefit of arteriovenous anastomosis in organic brain disease. Surgery is not difficult and involves only the production of a small fistula between the common carotid artery and the internal jugular vein is tied off and cut so as to prevent arterial blood from returning directly to the heart. Arterial blood thus traverses both the vein and the artery.

BLOOD SUPPLY OF THE BRAIN

Cobb¹ has shown that the venous system, as well as the arterial supply of the brain, anastomoses extensively. He has stated that end arteries do not exist in the brain and that all parts of the brain are connected by an intercommunicating network of vessels. Therefore, arterial blood under arterial pressure in the venous system would result in a redistribution of blood flow.

Venous return from the brain is known to be asymmetrical. Although the sinuses of the brain have several communications, there is a definite pathway of blood from each sinus to reach one of the internal jugular veins. The superior sagittal sinus commences at the foramen caecum, courses back in the midline just beneath the skull to the internal occipital protuberance. Here it deviates sharply to the right and continues as the corresponding transverse sinus and eventually

From the Department of Surgery and the Department of Pediatrics, Western Reserve University School of Medicine and Babies and Children's Hospital of Cleveland. Presented at the Fifty-Ninth Annual Meeting of the American Pediatric Society, Atlantic City, N. J., May 6, 1949.

becomes the right internal jugular vein. The inferior sagittal sinus runs through the center of the brain to the left transverse sinus and finally the left internal jugular vein. Essentially, blood destined to reach the right jugular vein drains the cerebral cortex and that reaching the left jugular comes from the deeper portions and cerebellum. Most of the drainage follows the above pattern, but Bailey² has demonstrated an appreciable anastomosis between superficial and deep venous systems. His findings have been confirmed by our work. We injected a tracer substance into the right and left internal jugular veins and into the common carotid arteries. Under arterial pressure, the colored mixture injected into the right jugular vein filled the superior sagittal sinus and all of its visible branches. Colored material was also noted to enter the deep circulation but not through the torcular Herophili. Operation upon the right side would contribute the majority of blood to the cortex and also significant amounts to the deep circulation. All of our operations have, as a result, been performed on the right side. Fig. 1 illustrates the venous tributaries of the superior sagittal sinus that would fill with arterial blood postoperatively.

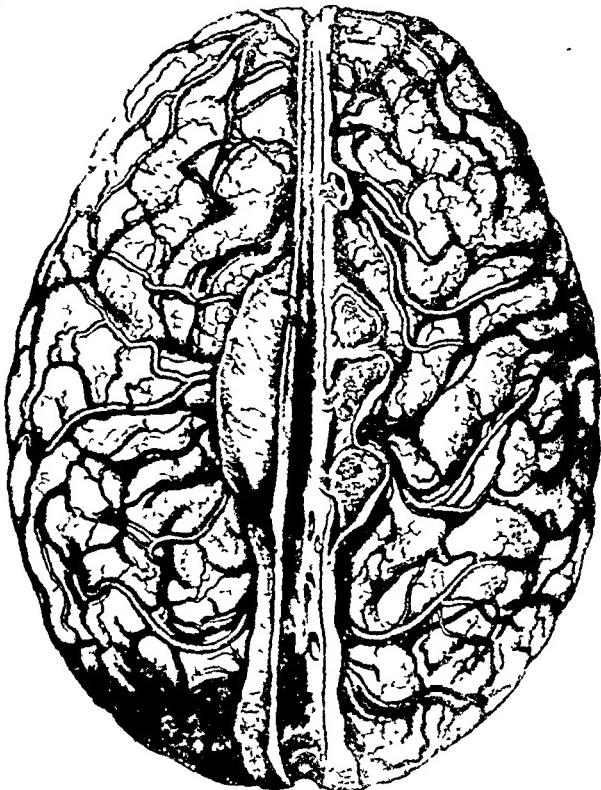


Fig. 1.—Venous tributaries of the superior sagittal sinus that filled with the tracer dye following injection of the right internal jugular vein. (Courtesy, The Macmillan Company, An Atlas of Human Anatomy, page 690, FIG. 1085.)

PHYSIOLOGY OF ARTERIOVENOUS ANASTOMOSES

Arteriovenous fistulas present the theoretical problem of pathologic stress on the cardiovascular system. Cardiac hypertrophy results from large shunts of blood entering the venous system and right side of the heart under increased pressure. Such a condition does not exist as a result of this operation because the internal jugular vein proximal to the anastomosis is tied off. Bernheim,^{3, 4} after performing such an operation in the extremities, has found no cardiac complications to result in several cases, some followed as long as eighteen years.

Pulsating exophthalmos would appear to be a possible complication of carotid-jugular anastomosis. The clinical entity has been accurately described by Martin and Mabon⁵ in a summary of all previously reported cases. In the majority of these cases the internal carotid artery had ruptured directly into the cavernous sinus. Exuded blood at that point flows rapidly away through venous channels. Exophthalmos is caused by blood under arterial pressure within the cavernous sinus. No such pulsation followed our operation in any of eleven patients. Arterial blood reaching the cavernous sinus will be under such low pressure that the occurrence of this complication is not likely.

The experience of Sciaroni⁶ in performing a complete reversal of cerebral circulation in man has demonstrated a freedom from such complications due to the presence of arterial blood in the venous system. Venous channels carrying blood under arterial pressure tend to hypertrophy, as shown by Wolff.⁷ Danger of spontaneous rupture of veins should, therefore, be minimal. Such has also been the experience of Beck⁸ in surgery performed on the coronary veins. Two cases of congenital arteriovenous fistula between the common carotid artery and the internal jugular vein were reported by Ward and Horton.⁹ Both children, aged 5 years and 14 years, demonstrated no cerebral abnormality.

Effects on Tissues.—Shenkin and associates¹⁰ state that blood flow to the head or extremity distal to an arteriovenous fistula is markedly increased and may be as much as two or three times normal. In their review of forty-two pediatric cases with congenital or post-traumatic A-V fistulas of the head or extremities, Ward and Horton⁹ reported the following generalizations. The involved part distal to the fistula was larger, longer, or warmer than the comparable unininvolved part. We believe the same hypernutrition, due to increased blood supply, would result from our operation.

CEREBRAL VASCULAR CONTROL

Cerebral blood flow under normal conditions is maintained through three basic mechanisms. Wolff and Lennox¹¹ have shown that decreased oxygen and increased carbon-dioxide tensions in the blood stream give rise to increased cerebral blood flow. The mechanisms are through the carotid body as well as by a direct humoral action on the arterioles themselves. Bouchaert and Heymans¹² state that increased flow will result from decreased arterial pressure at the site of the carotid body. As a result of the division of the arterial supply following surgery, the blood pressure at the carotid body drops as much as 20 to 30 mm. mercury. Partial increase in flow may result from this mechanism. The major increase in flow has been shown by Wolff⁸ to come as a result of increased pres-

sure within the veins. In the redistribution of blood supply, dilatation may result from the direct action of carbon dioxide on the arterial side of the capillary.

PATHOLOGY OF CEREBRAL INJURY

Much work has been done to demonstrate the histopathology of brain injury. Brain injury caused by mechanical trauma, anoxia, hemorrhage, and vascular occlusion are all characterized pathologically by decreased blood flow and glial tissue proliferation. The clinical results are mental deficiency, convulsive disorders, and sensory-motor impairment.

Scarring occurs in any area of the brain which has been injured and in which sufficient blood supply has been maintained to allow for glial replacement. The neurons may be completely destroyed, may gradually die, or may continue to live in an obviously abnormal state due to insufficient nutrition. They do not multiply or hypertrophy.

Penfield and Erickson¹³ have most clearly shown the long-range sequence of cicatrization. Astrocytes and microglial cells normally limit themselves to the area immediately surrounding small blood vessels. Following injury the glial cells invade the area, microglial cells phagocytizing the dead tissue and the astrocytes replacing the same. Within the center of the scarred area there are no functioning neurons. There is no definite border to the zone of scarring. In the outer portions of the cicatrix viable neurons may be seen. Small blood vessels are abnormally few in number in this transition zone between normal and scar tissue, even though the larger vessels may be plentiful. The cerebral tissue in this area is not destroyed but is subjected to unfavorable circumstances with improper nourishment. Over a period of months and years the astrocytes increase in size and number with a resulting increase in the area of the scar. This is due to slow destruction of the scar. Penfield and Erickson¹³ state, "If a selective blood vessel stain be carried out on tissue from the central portion of an old scar, it is found that although vascular trunks stain, there is an almost complete lack of capillaries. If the normal gray matter be similarly studied, the capillary plexus is found to be very rich. The tissue from the intermediate zone of the gray matter contains numerous vessel trunks but is quite deficient in capillary bed, almost as deficient as the aganglionic core of the scar. This intermediate zone between brain and scar is the zone in which is found evidence of slowly progressive destruction." The signs of actively proliferating glial cells indicate an ischemic condition which may damage, irritate, and eventually destroy the ganglion cells of the area.

In addition to the decreased vascularity of the scar tissue, the glial cells themselves may serve as a barrier to adequate cellular nutrition. This has been established by the recent work of Manery¹⁴ on the controversial subject of blood-brain-barrier. Brain tissue does not allow the free diffusion of non-gaseous substances characteristic of most other body tissues. For example, Manery has shown that brain requires five or more hours to reach equilibrium with injected blood sodium. Other tissues require less than one hour for such equilibration. She has attributed this to the glial sheath that normally surrounds

cerebral vessels as well as to the normal glial framework of the brain itself. The glial tissue serves as a "protective barrier" and retards the diffusion of non-gaseous material. One would, therefore, expect increased resistance to diffusion in the presence of increased glial tissue.

VIABILITY AND FUNCTION OF NERVE TISSUE

The existence of viable but nonfunctioning neurons is suggested by the above findings of Penfield and Erickson. The fact that such a condition may exist has other experimental as well as clinical support. It is a common occurrence to see widespread involvement of the cerebrum following a cerebrovascular accident. After a period of weeks and months function may once again return to paralyzed parts. Severe hypertension, hypoglycemia, acidosis, depressing drugs may produce temporary as well as permanent loss of cell function. Loss of function for a long period of time may be followed by a partial or complete return to normal.

Adrian and Bronk¹⁵ have shown that peripheral as well as spinal nerve preparations can survive for long periods of time on a subnormal supply of oxygen and glucose. Survival is accomplished through the anaerobic lactic acid metabolism of central as well as peripheral neurons. Erlanger and associates¹⁶ have demonstrated that maximal stimulation may or may not cause such a fiber to discharge. For varying periods of time complete reversal is possible. Himmich,¹⁷ in working with brain slices, has shown their ability to function anaerobically through the mechanism of lactic acid metabolism. Aerobic and anaerobic metabolism is reversible for long periods of time at suboptimal blood levels. Under clinical conditions of acute as well as chronic cerebral anoxia, Proger¹⁸ has found almost immediate return or improvement of function with the administration of Cytochrome C.

REVASCULARIZATION OF THE BRAIN

Revascularization of cardiac muscle by introduction of arterial blood directly into the venous system has been accomplished by one of us (Beck).⁸ Improvement of blood supply has been demonstrated clinically and by histologic section. Such findings serve as a rational basis for seeking improvement of cerebral blood flow by arteriolization of the internal jugular vein.

Patients chosen for this operation have been those with types of organic brain injury which may ordinarily result in gliosis. In general, this includes patients showing mental retardation on an anoxic or arteriosclerotic basis. Patients with convulsive disorders on an organic basis have been selected, with and without mental retardation. Brain injury as a result of vascular occlusion or hemorrhage may also serve as an indication.

Operative Procedure.—A right-sided arteriovenous fistula between the common carotid artery and the internal jugular vein has been produced. The approach was through a transverse incision over the right side of the neck, about 2.0 cm. above the clavicle. The sternocleidomastoid muscle was cut and the internal jugular vein and the common carotid artery were dissected free for a distance of 4.0 cm. The jugular vein was ligated with three ligatures inferiorly and cut. It was temporarily ligated above, as was also the carotid ligated above

and below, allowing sufficient room to make the fistula. An opening of 4 to 5 mm. was made in both the artery and the vein. Consideration was taken, in forming the fistula, not to create too large or too small a defect which might have resulted respectively in heart failure or thrombosis. An over-and-over suture was used, a new suture being started at each end. The three temporary occluding sutures were then removed. Temporary leaking of blood was then stopped. The vein was noted to be red with arterial blood, and pulsation was observed in the artery distal to the fistula. Before the anastomosis was made, all branches of the jugular vein below the base of the skull were ligated. The sternocleidomastoid muscle was sutured together, and the platysma was closed, as was the skin.

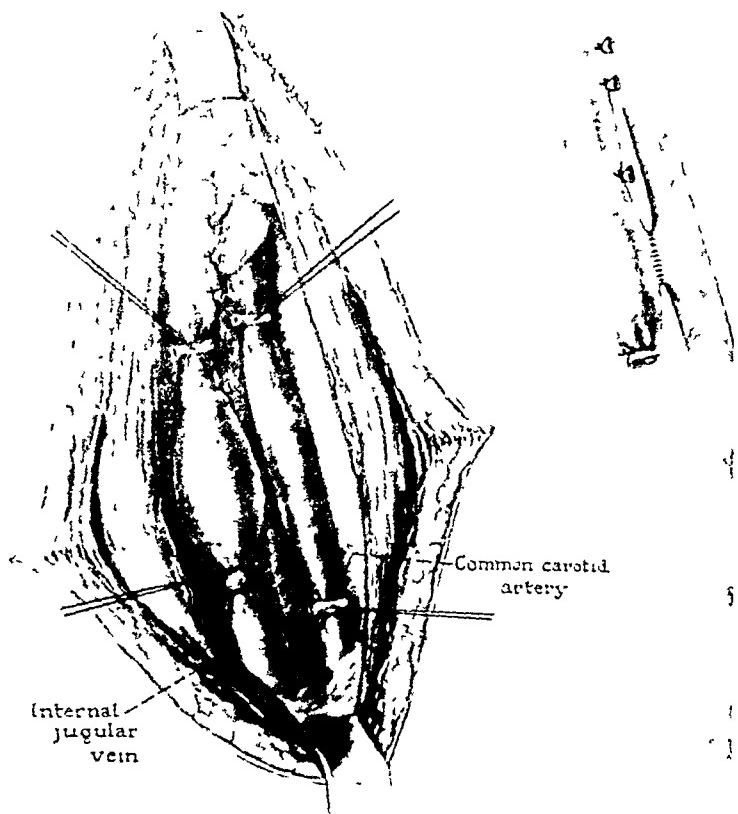


Fig. 2.—Illustration of operation.

The literature reports only one other operation performed with similar intent. Four patients, operated upon by Sciaroni,⁷ were subjected to a complete reversal of cerebral circulation on one or both sides of the neck. This was accomplished by anastomosing the cardiac part of the common carotid artery to the cephalic part of the internal jugular vein. Venous return is effected by

anastomosis of the cephalic part of the common carotid to the cardiac part of the internal jugular vein.

Three patients with hypertensive or arteriosclerotic cardiovascular disease resulting in cerebral pathology all demonstrated benefit by his complete reversal. The fourth patient, a post-traumatic epileptic, showed marked postoperative improvement. Although his operation undoubtedly results in some increase of cerebral blood flow, the resulting artificial shunt of arterial blood down the internal carotid artery from the Circle of Willis may result in loss to cerebral tissue of as much as one fourth of the blood in the Circle.

Eleven patients have been subjected to our procedure. Ten were children, ranging in age from 11 months to 14 years, and had mental retardation with or without a convulsive disorder. The eleventh was a 38-year-old adult with mental deterioration and a left hemiplegia.

The preoperative workup consisted of a complete neurologic examination including lumbar puncture. An electroencephalogram and pneumoencephalogram were done as both diagnostic procedures and reference points for post-operative studies. A psychometric examination was done, including the revised Stanford-Binet I.Q. test for children older than three years, Parts I, II, and III, depending on the age of the child. Development of children below three years was evaluated by the methods of Gesell.¹⁰

A rough quantitative test for measurement of cerebral blood flow has been devised. The individual, serving preoperatively as his own control, allows for a fairly accurate index of change in flow pre- and postoperatively. The principle of the test is based upon the time rate of uptake of a radioactive substance by the vascular tree of the brain. Following the rapid antecubital injection of 2.5 milliecuries per kilo of radioactive protein-bound iodine, a well-shielded Geiger counter measures the increasing count over one-half of the skull. A steadily rising curve is plotted by a continuous graph-recording galvanometer attachment to the Geiger counter. Lugol's solution is given at least a day before each test so as to fill the thyroid gland with iodine. Although the radioactive iodine has a half life of only eight days, administration of Lugol's solution prevents radiation of the thyroid. The procedure has been standardized against the nitrous oxide method for determining cerebral blood flow of Kety and Schmidt.²⁰ Therefore, an integral formula may be derived to give a rough quantitative measure of cerebral blood flow. The final formula is simple, but its derivation is beyond the scope of this paper and is the subject of a contemporary publication.

Values obtained from the test are comparable but are not exact indices of cerebral blood flow. The results serve as numerical indices for all patients subjected to the procedure. A typical set of pre- and postoperative curves are seen in Fig. 3 and apply to the third patient subjected to surgery.

Samples of arterial and internal jugular blood were drawn before surgery. Oxygen saturations were determined and the arteriovenous oxygen difference of the brain computed. Results obtained from ten of the patients receiving surgery are compared in Table 1 with results from ten children serving as controls. The latter were of normal intelligence and free of convulsive disorders.

Arterial blood was obtained from the femoral artery in the majority of cases and from the carotid artery in several of the younger patients at the time of surgery. Venous samples were always obtained before surgery. Arterial saturation has been found to change only slightly, if at all, during anesthesia if oxygenation of the blood is kept constant. Venous saturation will, however, vary markedly during anesthesia.

A significant difference was found to exist between the two groups. The over-all average of the controls was a difference of 6.1 vols. per cent, while that

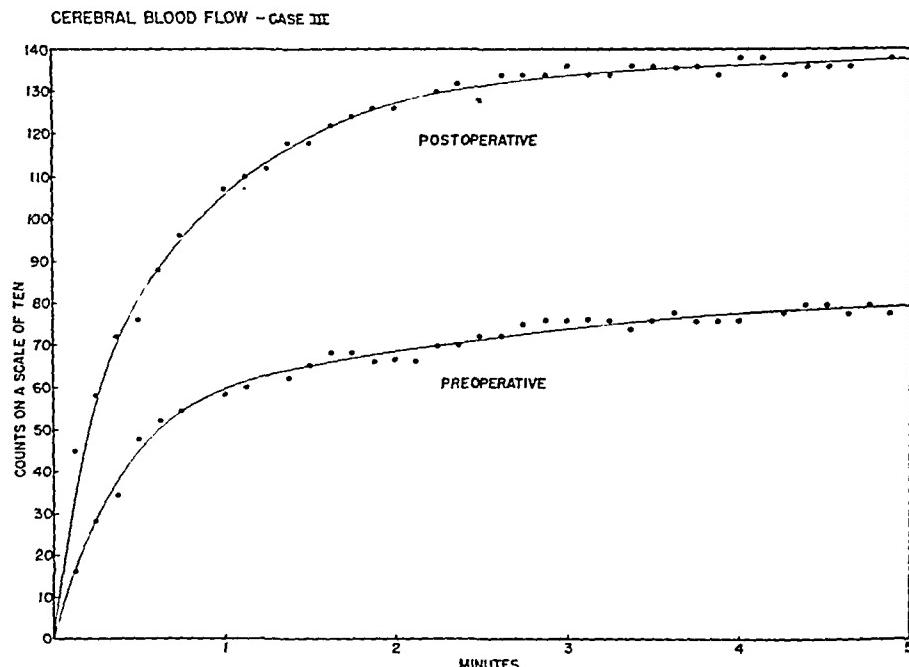


Fig. 3.—Preoperative and postoperative cerebral blood flow curves are plotted by a graph recording attachment to a Geiger counter. Note the marked increase in flow represented by the postoperative curve.

TABLE I. ARTERIOVENOUS OXYGEN DIFFERENCE IN A GROUP OF CONTROL CHILDREN AS COMPARED WITH A SERIES OF PATIENTS SUBSEQUENTLY OPERATED

CONTROLS			OPERATED CASES		
PATIENT	AGE	(A-V) O ₂ VOLS. %	PATIENT	AGE	(A-V) O ₂ VOLS. %
1	2 yr.	6.2	L. C.	4 yr.	6.8
2	18 mo.	5.4	T. S.	11 mo.	7.7
3	5 yr.	6.1	F. L.	18 mo.	7.2
4	12 yr.	6.3	B. F.	13 yr.	6.2
5	3.5 yr.	5.8	J. C.	5 yr.	7.7
6	22 mo.	5.5	B. D.	3 yr.	8.0
7	13 yr.	6.0	C. T.	2.5 yr.	7.3
8	8 yr.	6.8	S. S.	20 mo.	6.6
9	4 yr.	5.6	J. S.	14 yr.	6.5
10	2 yr.	6.4	G. H.	5 yr	7.2
Mean		6.1	Mean		7.1
Standard deviation of the individual differences		±0.35			±0.48

of the operated group was 7.1 vols. per cent. Lennox²¹ found an (A-V) O₂ difference of 6.5 vols. per cent to be nearly constant for patients of all age groups. Kety and Schmidt give the figure of 6.3 vols. per cent for the average normal difference of their series of adults. Results chemically confirm the histopathological findings of Penfield and Erickson.¹³ Viable cells in the presence of inadequate blood supply appear to consume more of the available oxygen than do cells under normal circumstances. These results serve as an additive indication for studying the effects of this operative procedure.

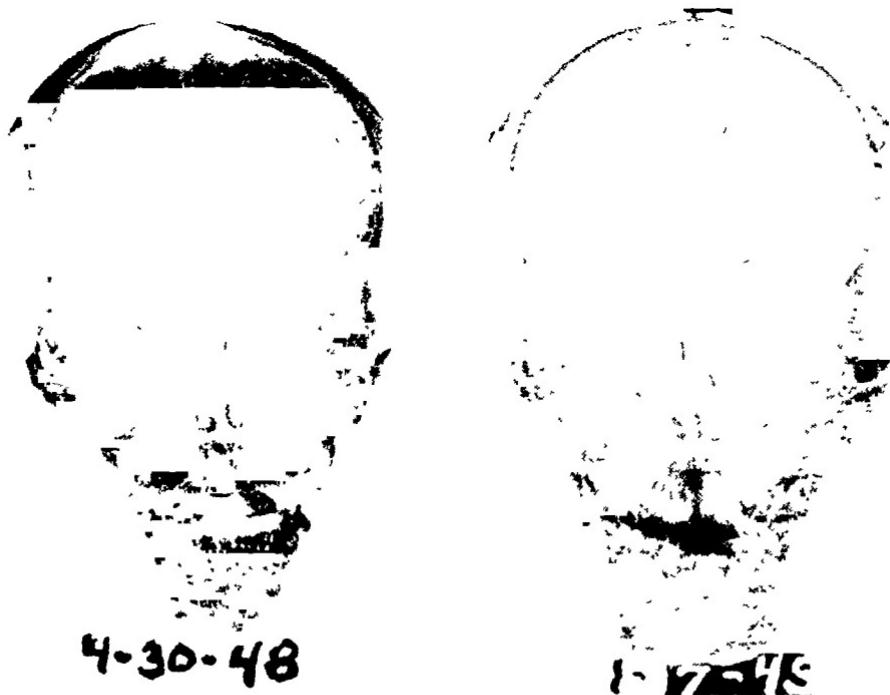


Fig. 4.—Skull films on Patient 1 taken before and two months after operation. The figure on the right demonstrates opening of the sagittal and lambdoidal sutures compared with the closed state of the sutures on the left film.

CASE REPORTS

CASE 1.—N. N., a 23-month-old white female infant, was first seen at 13 months of age. She was the product of a normal, full-term pregnancy, normal labor and delivery, but weighed only 4.75 pounds at birth. The baby was stated to have been 20.5 inches long, but very thin. No instruments were used. The umbilical cord was said to have been abnormal, but a description of the cord and placenta could not be obtained. There was no cyanosis or jaundice in the neonatal period. She took feedings poorly and vomited frequently. Crying was infrequent and parents state that she was a "very good baby." At 5 months of age the parents were convinced of the infant's retardation. In the first year of life she did not sit up, did not reach for objects, was not interested in toys, did not follow objects, and occasionally developed crossing of her eyes.

Physical examination at 13 months of age demonstrated her abilities, developmentally, to do everything on a 3-month level and some things on a 4-month

level but nothing on a 5-month level. The anterior fontanel was closed and, according to the parents, had been so for some time. The head measured 42.5 cm., while the chest measured 47.5 cm. There was an internal strabismus of the left eye.

She was admitted to Babies and Children's Hospital on November 9, 1948, at the age of 19 months. Improvement in development was noted to a 5-month level. X-rays of the skull at 13 and 19 months showed premature closure of all sutures. Pneumoencephalograms showed moderate cortical atrophy and hydrocephalus ex-vacuo.

On Nov. 12, 1948, a right-sided A-V fistula was produced between the common carotid artery and the internal jugular vein.

After surgery, cyanosis of the right side of the face and the right retina was noted. This cleared in twelve hours. The spinal fluid pressure rose to 375, but fell to 150 by discharge on the ninth postoperative day. The blood pressure fell to 80/60 after operation, but returned to 90/65 by discharge. No change in pulse rate was noted.

The patient was seen two months postoperatively, at which time head size had increased to 45 cm. and the cranial sutures had reopened. A comparison of the pre- and postoperative films is seen in Fig. 4. Developmentally she could perform on a 7-month level. For the first time she was sitting without support and drinking from a cup. Interest in toys was also on a 7-month level. Examination five months after operation revealed even further improvement. The strabismus was no longer evident and play was active. A chest film revealed no change in size or shape of the cardiac pattern.

CASE 2.—R. J., a 38-year-old white man, was admitted to Crile Veterans' Hospital Jan. 4, 1949, with the following history. He was stated to have shown signs of mental deterioration and personality change three months before admission. Characteristically of a cheerful nature, he became moody and irritable. An intermittent frontal headache was an additional complaint. Two weeks before entry, sudden onset of dizziness was noted and was followed by paralysis of the left side of the body.

Physical examination revealed a middle-aged white man of average nutrition and build. Signs of mental deterioration were marked, speech was absent, and the entire left side of his body was paralyzed. The blood pressure was 160/90.

Spinal fluid was normal. An arteriogram demonstrated a block of the right internal carotid artery at the second cervical vertebra. Pneumoencephalograms showed bilateral cortical atrophy, more marked over the parietal areas. A right parietal focus was evident by electroencephalography.

A diagnosis of right internal carotid artery thrombosis was made. During the next month his neurological condition went progressively downhill. Cortical function was at a minimum. On Feb. 3, 1949, a right-sided arteriovenous anastomosis was performed between the carotid and the jugular vein.

Four days after surgery his sensorium showed marked clearing and speech began to return. At the end of the first postoperative week he was able to move his left side because of partial return of motor function. At the end of three months he had regained most of his motor function, including speech. An electroencephalogram showed marked improvement, characterized by disappearance of most of the 3 to 4 per second, high-voltage, slow-wave dysrhythmia. The right parietal focus was still present but less marked.

CASE 3.—J. C., a 4-year-old white male, presented an abnormal history dating from birth. Labor was difficult, requiring incision of the cervix for completion. The neonatal period was complicated by cyanosis requiring oxygen. Development was retarded. He sat at the age of 8 months, stood with support

at one year, but did not walk until 19 months. Speech started at the age of 2.5 years. From the age of 16 months he had been having generalized grand mal convulsions as frequently as 5 to 8 per day. To the time of admission, these had not been controlled by adequate doses of phenobarbital, "dilantin," or "tri-dione." After admission he was completely controlled on 0.1 gm. "mesantoin" three times daily.

Physical examination was negative except for his obvious mental retardation. Mental age by psychometric examination was 2 years and 10 months at the chronological age of 3 years and 10 months. Pneumoencephalography revealed a moderate degree of generalized cortical atrophy. A generalized 3 per second electroencephalographic dysrhythmia was an additional finding. A graphic representation of his cerebral blood flow is seen in Fig. 3.

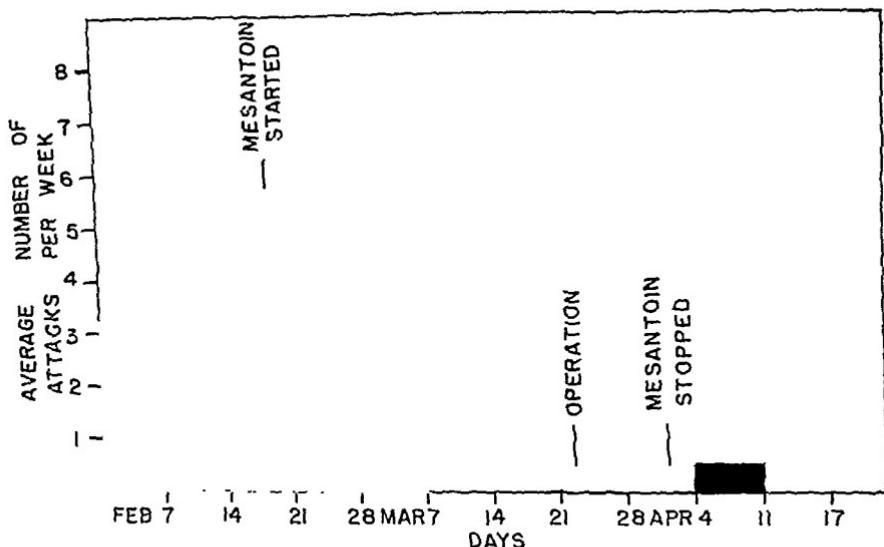


Fig. 5.—Average preoperative and postoperative grand mal attack rate per week in Patient 3.

Operation was performed on March 22, 1949. An immediate postoperative finding was right-sided retinal cyanosis and congestion of the retinal veins. The veins were observed to carry arterial blood. Cyanosis cleared in twelve hours. Spinal fluid pressure rose postoperatively from 150 mm. to 275, but returned to 160 by the end of the first week. "Mesantoin" was stopped on the tenth postoperative day. On the fifth and sixth day after cessation of the drug he had two grand mal seizures, apparently due to withdrawal. Since then he has been free of attacks and his general behavior has noticeably improved. His pre- and postoperative attack rate is shown in Fig. 5. As shown in Fig. 3, his postoperative cerebral blood flow approximately doubled.

CASE 4.—T. C., an 11-month-old white male infant, had been followed by us since the age of 3 months. He was apparently well prior to two months of age and was born after a normal full-term pregnancy, by normal labor and delivery. At the age of 2 months he had a generalized grand mal convolution. He was admitted to another hospital. There was no associated fever, but a lumbar puncture showed increased protein and cells. The spinal fluid was normal three days later, but up to the time of surgery he was having two to five generalized grand mal convulsions daily.

His pneumoencephalogram showed marked cortical atrophy and resultant moderate hydrocephalus ex-vacuo. Electroencephalogram was markedly abnormal with generalized, high-voltage, 2 to 3 per second waves. Developmental quotient by the Gesell method was 15. The operation was performed on April 1, 1949. Retinal cyanosis cleared after twenty-four hours. The blood pressure rose to 158/106 postoperatively, but returned to 95/60 after one week. A corresponding rise and return of the pulse rate was noted. Spinal fluid pressure rose from 220 mm. to 350, but fell to 250 by the end of the first week. Following surgery, his attack rate has fallen to only an occasional grand mal episode, without the addition of the preoperative dose of 32 mg. of phenobarbital t.i.d. Generally he appears more active.

DISCUSSION AND SUMMARY

Four of the eleven patients subjected to the operation have been presented. Operations on the other seven patients were performed just prior to the writing of this paper and therefore their progress could not be evaluated. The four patients described above all demonstrated early and progressive postoperative improvement. Although the postoperative follow-up is limited to one, three, and five months, benefit has been obvious. We believe this procedure represents the first successful attempt at correction of mental retardation on an organic basis. Complete restoration of normal function cannot be anticipated; rather expectation should be limited to some return of function of remaining viable neuronal tissue.

The operation has proved to be safe. Complications have, as yet, not appeared. No difficulty has been encountered in reference to pulsating exophthalmos, increased intracranial pressure, or cardiac hypertrophy. Furthermore, should untoward results appear, the fistula could be closed.

The procedure is in the stage of more extensive trial and should be considered as representing a new approach to a problem rather than as an acceptable and complete solution.

REFERENCES

1. Cobb, Stanley: The Cerebral Circulation XIII: The Question of End-Arteries of the Brain and the Mechanism of Infarction, *Arch. Neurol. & Psychiat.* 25: 273-280, 1931.
2. Bailey, P.: Peculiarities of the Intracranial Venous System and Their Clinical Significance, *Arch. Neurol. & Psychiat.* 32: 1105, 1934.
3. Bernheim, B. M.: Arteriovenous Anastomoses: Successful Reversal of Circulation in All Four Extremities of the Same Individual, *J. A. M. A.* 60: 360-362, 1913.
4. Bernheim, B. M.: Arteriovenous Anastomosis: Follow-up After Eighteen Years of "Successful Reversal of the Circulation in All Four Extremities of the Same Individual," *J. A. M. A.* 96: 1296-1297, 1931.
5. Martin, J. D., Jr., and Mabon, R. F.: Pulsating Exophthalmos: Review of All Reported Cases, *J. A. M. A.* 121: 330-335, 1943.
6. Sciaroni, G. H.: Reversal of Circulation of the Brain, *Am. J. Surg.* 76: 150-164, 1948.
7. Wolff, H. G.: The Cerebral Circulation, *Physiol. Rev.* 16: 545-596, 1936.
8. Beck, Claude S.: Revascularization of the Heart, *Ann. Surg.* 128: 854-864, 1948.
9. Ward, G. E., and Horton, B. T.: Congenital Arteriovenous Fistulas in Children, *J. Pediat.* 16: 746-766, 1940.
10. Shenkin, H. A., Spitz, E. B., Grant, F. C., and Kety, S. S.: Physiologic Studies of Arteriovenous Anomalies of the Brain, *J. Neurosurg.* 5: 165-172, 1948.
11. Wolff, H. G., Lennox, W. G.: Cerebral Circulation, XII: The Effect on Pial Vessels of Variations in the Oxygen and Carbon-Dioxide Content of the Blood, *Arch. Neurol. & Psychiat.* 23: 1097, 1930.

12. Bouchaert, J. J., and Heymans, C.: Carotid Sinus Reflexes: Influences of Central Blood Pressure and Blood Supply on Respiratory and Vasomotor Centers, *J. Physiol.* 79: 49, 1933.
13. Penfield, W., and Erickson, T. C.: Epilepsy and Cerebral Localization, Springfield, 1941, Charles C Thomas.
14. Manery, J. F., and Haege, L. F.: The Extent to Which Radioactive Chloride Penetrates Tissues, and Its Significance, *Am. J. Physiol.* 134: 83-93, 1941.
15. Adrian, E. D., and Bronk, D. W.: The Discharges of Impulses in Motor Nerve Fibres: I. Impulses in Single Fibres of the Phrenic Nerve, *J. Physiol.* 66: 81, 1928.
16. Erlanger, J., Bishop, G. H., and Gasser, H. S.: Experimental Analysis of the Simple Action Potential Wave in Nerve by the Cathode Ray Oscillograph, *Am. J. Physiol.* 78: 537, 1926.
17. Himwich, H. E., and associates: The Respiratory Quotient of the Brain, *Am. J. Physiol.* 101: 446, 1932.
18. Proger, S., and Decaneas, D. J.: Some Further Observations on the Parenteral Use of Cytochrome-C With Special Reference to Cerebral Anoxia and Shock, *Bull. New England M. Center.* 7: 149-151, 1945.
19. Gesell, A.: Developmental Diagnosis, New York, 1945, Paul B. Hoeber, Inc.
20. Kety, S. S., and Schmidt, C. F.: The Nitrous Oxide Method for the Quantitative Determination of Cerebral Blood Flow in Man: Theory, Procedure, and Normal Values, *J. Clin. Investigation* 27: 476-483, 1948.
21. Lennox, W. G.: Constancy of the Cerebral Blood Flow, *Arch. Neurol. & Psychiat.* 36: 375, 1936.

THE ACTION OF AUREOMYCIN, OF POLYMYXIN B, AND OF STREPTOMYCIN IN EXPERIMENTAL MURINE PERTUSSIS

WILLIAM L. BRADFORD, M.D., AND ELIZABETH DAY, M.S.
ROCHESTER, N. Y.

THE purpose of this paper is to describe the action of aureomycin on experimental infection of mice with *Hemophilus pertussis*, and to compare the results with those obtained by previous experiments with Polymyxin B and with streptomycin.

Previous reports from our laboratory¹ and from that of Hegarty² have indicated favorable effects of streptomycin used against the experimental disease in mice. Favorable reports of its effect on the clinical disease have been made by Coffey and Levy,³ Dowling,⁴ Leichenger and Schultz,⁵ and Gordon and Almaden.⁶ In a small group of cases of pertussis treated with streptomycin we observed that the organism disappeared from the respiratory tract more rapidly than it did in a group of untreated cases, particularly when the drug was administered as an aerosol.⁷ Schwabacher, Wilkinson, and Karran⁸ recently reported that streptomycin failed to exert a beneficial effect on the disease.

Both aerosporin, derived from a culture of *Bacillus aerosporus Greer* isolated by Ainsworth, Brown, and Brownlee,⁹ and a similar, but not identical antibiotic, polymyxin, derived from filtrates of cultures of *Bacillus polymyxa* by Benedict and Langlykke,¹⁰ and by Stansby, Shepherd, and White,¹¹ have been found to possess in vitro as well as in vivo effectiveness against *H. pertussis*. While observers have found polymyxin to be from five to ten times more effective than streptomycin, they have also found it to be more toxic than streptomycin; in fact, it has been withdrawn recently from clinical usage for the purpose of further study.

Aureomycin is an antibiotic obtained by Duggar from the mold *Streptomyces aureofaciens*. Its history, characteristics, and action on a number of experimental and clinical infections have been described recently by Duggar and others.¹² Among its interesting characteristics may be mentioned the following:

Rapid absorption into the blood after oral administration.

Rapid deterioration in alkaline or even neutral solutions, including the usual body fluids.

Effective urinary concentration after oral administration, which persists for at least three days.

Effectiveness against gram-negative as well as gram-positive organisms, and against certain viruses and rickettsiae.

From the Department of Pediatrics, University of Rochester School of Medicine and Dentistry.

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Relatively low toxicity and infrequency with which organisms become resistant to it.

A bacteriostatic rather than bactericidal action.

The name aureomycin indicates in part the yellow color of the product.

PROCEDURE

Sensitivity of *H. pertussis* to aureomycin was tested in solid medium. The antibiotic was incorporated, in varying concentrations, into the Bordet medium at the time plates were poured. When the medium solidified, its surface was streaked with a standard loopful of a freshly prepared suspension of organisms containing 10 billion bacteria per milliliter. The degree of growth was observed after incubation for seventy-two hours at 37° C.

To test the action of the drug against the experimental disease, 3-week-old white Swiss mice were infected by dropping 0.05 ml. of a standardized suspension of freshly isolated organisms containing 10 billion bacteria per milliliter, into the nares, according to the technique used in our laboratory for several years.¹² Thus each mouse received approximately 500 million organisms. As determined by a simultaneously run test in other mice, this inoculation proved to be 250 times the dose (2 million) required to kill 50 per cent of the mice. In one experiment, groups of mice, ten in each, were injected intra-abdominally with varying amounts of aureomycin once daily for five days. The number of mice surviving at the end of the five-day period was recorded.

In other protective tests, groups of mice were arranged in subgroups of four each. The members of each subgroup received 0.05 ml. of a fourfold dilution of the bacterial suspension containing 10 billion organisms per milliliter. The number of deaths occurring in the twelve-day period after injection was recorded. The MLD (number of organisms in millions required to kill 50 per cent of the mice) was calculated by the method of Reed and Muench.¹⁴ Treatment, started six hours after injection, was given intra-abdominally daily for three days.

Similar technique was employed in testing the effect of Polymyxin B and streptomycin.

DISCUSSION OF RESULTS

Under the conditions of the experiment it is clear that from 25 to 50 µg of aureomycin per milliliter of solid medium were required to inhibit the growth of *H. pertussis* (Table I). With similar technique the organism was found to be sensitive to concentrations of streptomycin ranging from 0.4 to 1.2 µg per milliliter. In the case of polymyxin, 0.5 to 1 µg per milliliter was required.

TABLE I. SENSITIVITY OF *H. PERTUSSIS* TO AUREOMYCIN IN SOLID MEDIUM

STRAIN	µG AUREOMYCIN PER ML. MEDIUM				
	100	50	25	12.5	6.25
WT	0	0	++	+++	+++
SI	0	0	0	++	+++
SI. L.	0	0	++	++	+++
SIM	0	0	++	++	++
CO	0	0	++	++	++
MO	0	0	+	+++	+++

The rather high concentration of aureomycin required to inhibit growth is, no doubt, explained in part by the tendency of the substance to deteriorate. On the other hand, since at least forty-eight hours is required for growth of *H. pertussis*, during which time considerable deterioration occurs, it is probable that this method really reflects a bactericidal rather than bacteriostatic action.

ACTION OF AUREOMYCIN AGAINST *H. PERTUSSIS*

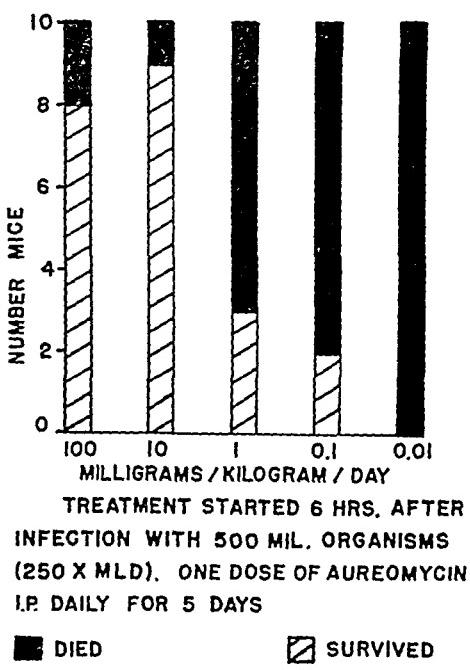


Chart 1.

In the in vivo tests (Chart 1) it is apparent that doses from 10 to 100 mg. per kilogram of body weight saved 90 per cent of the mice during the period of active therapy. When a dose of 100 mg. per kilogram per day was given for three days, significant protection was observed at the end of the seventh day (Table II). This was also true when aureomycin was given orally in the drinking water in a concentration of 25 mg. per milliliter. That the in vivo action of aureomycin is inhibitory rather than bactericidal is supported by the fact that, during the second week of observation, after treatment had been discontinued, many of the mice died. This, finally, is further illustrated by the data in Table III, where it is apparent that even a dose of 200 mg. per kilogram of weight gave only protection of a moderate degree. Furthermore, doses of from 10 to 100 mg. per kilogram of weight administered for only the first three days resulted in a very low percentage of negative lung cultures in the surviving mice. It is probable, of course, that continuation of therapy might have resulted in better clearance of the organism from the lungs and therefore better protection against death.

TABLE II. EFFECT OF AUREOMYCIN ON EXPERIMENTAL MURINE PERTUSSIS

AUREOMYCIN	DOSE OF ORGANISMS IN MILLIONS	DISTRIBUTION OF DEATHS ACCORDING TO DAY AFTER INFECTION													MLD*
		1	2	3	4	5	6	7	8	9	10	11	12	13	
100 mg./kg. daily intra-abdominally for 5 days	500										1		2	1	>500
	125										1			3	
	31.2							1					1	2	
	7.8										1			3	
250 mg./10 c.c. water ad lib orally for 5 days	500		1								2			1	0
	125											1		3	0
	31.2								1			2		1	
	7.8										1		2	1	
Controls	500			1	3										0
	125					1	2								1
	31.2							1						1	2
	7.8								2					2	
	1.9									1		2			1
															12.1

*Number survivors.

†Number of organisms in millions required to kill 50 per cent of the mice within seven days.

TABLE III. EFFECT OF AUREOMYCIN ON EXPERIMENTAL PERTUSSIS

AUREOMYCIN DAILY DOSE (3 DAYS)	NO. SURVIVING MICE DOSE OF ORGANISM IN MILLIONS					% NEGATIVE LUNG CULTURES	MLD*
	500	125	31.2	7.8	1.9		
10 Mg./kg.	0	0	1	2	3	0	7.8
Controls	0	1	1	1	2	0	4.6
100 Mg./kg.	0	2	1	1	1	20	4.2
200 Mg./kg.	1	3	4	3	3	—	125
Controls	0	1	0	3	4	43	14.9

*Number of organisms in millions required to kill 50 per cent of the mice.

TABLE IV. EFFECT OF POLYMYXIN B. ON EXPERIMENTAL MURINE PERTUSSIS

POLYMYXIN B DAILY DOSE (3 DAYS)	NO. SURVIVING MICE DOSE OF ORGANISMS IN MILLIONS					% NEGATIVE LUNG CULTURES	MLD*
	500	125	31.2	7.8	1.9		
10 Mg./kg.	3	4	4	4	3	80	>500
Controls	0	1	1	1	2	0	4.6
10 Mg./kg.	3	3	4	4	3	100	500
1 Mg./kg.	1	3	4	4	3	64	196
Controls	0	1	0	3	4	43	14.9

*Number of organisms in millions required to kill 50 per cent of the mice.

TABLE V. EFFECT OF STREPTOMYCIN ON EXPERIMENTAL MURINE PERTUSSIS

STREPTOMYCIN DAILY DOSE (3 DAYS)	NO. SURVIVING MICE DOSE OF ORGANISMS IN MILLIONS					% NEGATIVE LUNG CULTURES	MLD*
	125	31.2	7.8	1.9	0.47		
50 Mg./kg.	3	4	4	4	4	75	>125
Controls	0	1	4	3	3	18	12.7
100 Mg./kg.	4	4	4	4	4	100	>125
Controls	0	0	1	1	3	20	1.2
	500	125	31.2	7.8	1.9		
100 Mg./kg.	4	4	4	4	4	100	>500
Controls	0	1	1	1	2	0	4.6

*Number of organisms in millions required to kill 50 per cent of the mice.

In the case of polymyxin, it is clear that 10 mg. per kilogram per day gave definite protection (Table IV) and resulted in a high percentage (80 to 100 per cent) of negative lung cultures in the surviving mice.

Similar results were observed after treatment with streptomycin in doses of from 50 to 100 mg. per kilogram per day (Table V).

SUMMARY

Aureomycin in concentration of from 25 to 50 μg per milliliter of solid medium inhibited the growth of *H. pertussis*. Daily doses of 10 and 100 mg. per kilogram per day protected mice during the period of treatment, against 250 MLD of the organism instilled intranasally. The action appeared to be bacteriostatic rather than bactericidal, for deaths frequently occurred within ten days after cessation of therapy.

Polymyxin B in concentrations of from 0.5 to 1.0 μg per milliliter of solid medium inhibited the growth of *H. pertussis*. Daily doses of 1 mg. and of 10 mg. per kilogram of weight protected mice against the experimental disease.

H. pertussis was found to be sensitive to streptomycin in concentrations of from 0.4 to 1.2 μg per milliliter of solid medium, and protected mice against the experimental disease in therapeutic daily doses of from 50 to 100 mg. per kilogram of weight.

REFERENCES

1. Bradford, W. L., and Day, E.: Therapeutic Effect of Streptomycin in Experimental Murine Pertussis, *Proc. Soc. Exper. Biol. & Med.* 60: 324, 1945.
2. Hegarty, C. P., Thiele, E., and Verwey, W. F.: The *In Vitro* and *In Vivo* Activity of Streptomycin Against *H. pertussis*, *J. Bact.* 50: 651, 1945.
3. Coffey, J. D., and Levy, H. B.: Streptomycin in the Treatment of Pertussis Pneumonia, *Mississippi Doctor* 25: 295, 1948.
4. Dowling, H. F.: The Acute Bacterial Diseases, Philadelphia, 1948, W. B. Saunders Co., p. 339.
5. Leichenger, H., and Schultz, A.: Streptomycin in the Treatment of Pertussis, *J. PEDIAT.* 33: 552, 1948.
6. Gordon, V. H., and Almaden, P. J.: Streptomycin Therapy for Pertussis, *J. PEDIAT.* 34: 279, 1949.
7. Bradford, W. L.: Recent Contributions to the Diagnosis and Treatment of Pertussis, *N. Y. State J. Med.* 49: 397, 1949.
8. Schwabacher, H.: Wilkinson, R. H., and Karran, C. W. C.: Streptomycin in Whooping Cough, *Lancet* 1: 180, 1949.
9. Ainsworth, G. C., Brown, A. M., and Brownlee, G.: 'Aerosporin,' an Antibiotic Produced by *Bacillus aerosporus Greer*, *Nature London* 160: 263, 1947.
10. Benedict, R. G., and Langlykke, A. F.: Antibiotic Activity of *Bacillus polymyxa*, *J. Bact.* 54: 24, 1947.
11. Stansly, P. G., Shepherd, R. D., and White, H. J.: Polymyxin: A New Chemotherapeutic Agent, *Bull. Johns Hopkins Hosp.* 81: 43, 1947.
12. Duggar, B. M., and co-authors: Aureomycin, A New Antibiotic, *Ann. N. Y. Acad. Sci.* 51: Art. 2, p. 175.
13. Bradford, W. L., Brooks, A. M., and Katsampes, C. P.: The Therapeutic Effect of Sulfadiazine, and Immune Rabbit Serum in Experimental Murine Pertussis, *Yale J. Biol. and Med.* 16: 435, 1944.
14. Reed, L. J., and Muench, H.: A Simple Method of Estimating Fifty-per-cent End-points, *Am. J. Hyg.* 27: 493, 1938.

HEREDOPATIIA ATACTICA POLYNEURITIFORMIS IN CHILDREN

A PRELIMINARY COMMUNICATION

S. REFSUM, M.D., L. SALOMONSEN, M.D., AND M. SKATVEDT, M.D.
OSLO, NORWAY

IN the spring of 1947 four children presenting a clinical picture apparently not hitherto described in children, were admitted to the pediatric department of the Rikshospital.

Cases 1 and 2 were boy and girl twins with no other brothers or sisters. Their paternal grandmother and the grandfather of their mother were sister and brother. (See Fig. 1.) Case 3, a boy, was an only child and, as far as we know, his parents were not related to each other. Case 4 was a girl whose parents were first cousins. Her half-sister was healthy. These three families were not related to one another.

The case records of all four patients were much alike. In Cases 1, 2 and 3 the symptoms began at the age of 7 years, and in Case 4 they began at the age of 4 years. The onset was insidious with loss of appetite, an unsteady gait, dryness and desquamation of the skin, and progressive deafness.

CASE 1.—A girl twin weighed 2,000 Gm. when born on May 16, 1938. Physical and mental development normal.

Anorexia had been noticed since the summer of 1946. Her gait became unsteady and she stumbled easily. The skin became rough and hyperkeratotic. Some deafness had been observed in January, 1947.

She was admitted on March 20, 1947, and found to be puny and thin. Her intelligence was normal. The skin everywhere was dry and slightly desquamating, being thickened over the patella and bones of the elbow, where it was rough, desquamating, and of a dirty brown color.

There was bilateral diminution of hearing of neurogenic type. Only a high-pitched voice close to the ears could be heard. Tympana were normal.

Ophthalmoscopic Examination.—The fundus was defective in pigment, the vessels of the choroid showing through it. The pigmentation of the fundus was pathologic on both sides, with a hint of "pepper and salt." Vision was 5/5 on both sides. The field of vision was not examined.

Neurological Examination.—There was general weakness, notably in the distal parts of the limbs, with hypotonic muscles and loss of tendon reflexes. Gait was ataxic. Romberg's sign was positive. There was no nystagmus. Sensation was normal, with no increased tenderness on deep pressure, and normal vibration sense.

Electrocardiographic Examination.—The rate was 110; PQ 0.15 sec.; QRS 0.09 sec.; Q-T 0.34 sec.; $T_1 +$; $T_2 +$; $T_3 -$; $T_4 +$. All the figures were about the upper limit of the normal for age and frequency according to Ashmann's and Hull's tables (Q-T 0.325 sec. the upper normal limit).

From the Pediatric Department, University of Oslo. (The Rikshospital), Oslo, Norway;
Chief of Service, Professor L. Salomonsen, Dr. med.

The somatic examination showed nothing else pathologic. Wassermann test was negative. Blood count and serum proteins were normal. Gastric acidity was normal. A radiographic examination of the cranium showed normal conditions and nothing abnormal in hands and feet apart from the metatarsal bones of the fourth toe, which were short on both sides.

At first we suspected a vitamin B deficiency, but large doses of vitamin B preparations proved ineffectual, and there was no change in her skin. During her three-month stay in the hospital she became almost completely deaf. In other respects there was practically no change in her condition.

On her readmission to hospital in September, 1947, considerable deterioration in her general condition was observed. She might almost be said to be eacanthic: emaciation was extreme and she presented several small bed sores. Her atrophic skin was dry and desquamating and as thin as tissue paper in certain places. She was now completely deaf and the fundi showed the same pigment changes. On a neurological examination severe general atrophy of the muscles, general pareses, and absence of the deep reflexes of all the limbs were found.

She was treated with blood transfusions. Bronchopneumonia developed, and she died in a state of marasmus (see the post-mortem findings).

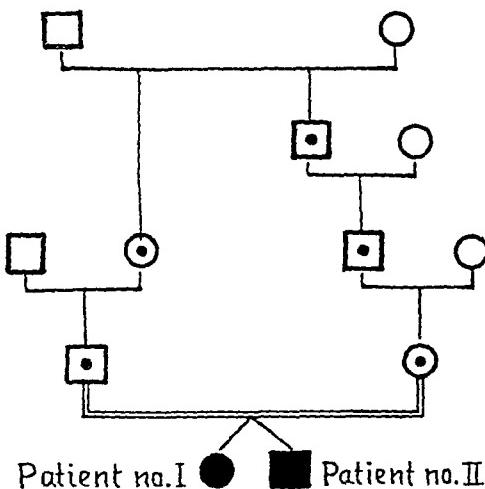


Fig. 1.—Pedigree of Cases 1 and 2, who suffered from heredopathia atactica polyneuropathica. The children twin brother and sister, are the offspring of a consanguineous marriage which suggests recessive heredity.

The symbols \blacksquare and \circ indicate probable heterozygous male and female individuals.

CASE 2.—A boy, the twin brother of the first patient, weighed 2,250 Gm. at birth. Physical and mental development were normal.

His illness developed simultaneously and with the same manifestations as those of his sister.

He was admitted on April 16, 1947, and found to be puny and thin. Intelligence was normal with an I.Q. of 94.2.

The skin was dry and desquamating, particularly over the limbs and back; in places it was thin and with an atrophic shine.

Bilateral diminution of hearing of the neurogenic type was found.

Fundi were somewhat poor in pigment with the result that the choroid vessels were visible through them. Small patches without pigment occurred

in both maculae. The optic discs were normal. Vision was 5/5 on both sides. The field of vision was normal.

Neurological Examination.—General reduction of muscle tone with weakness was most marked in the distal parts of the limbs. The deep reflexes of arms and legs were weak or absent. Plantar reflexes were normal. There was no ataxia. Romberg's sign was negative. In sensation, there was no definite loss of the superficial modalities, normal vibration sense, and sense of position. Deep tenderness on pressure was normal.

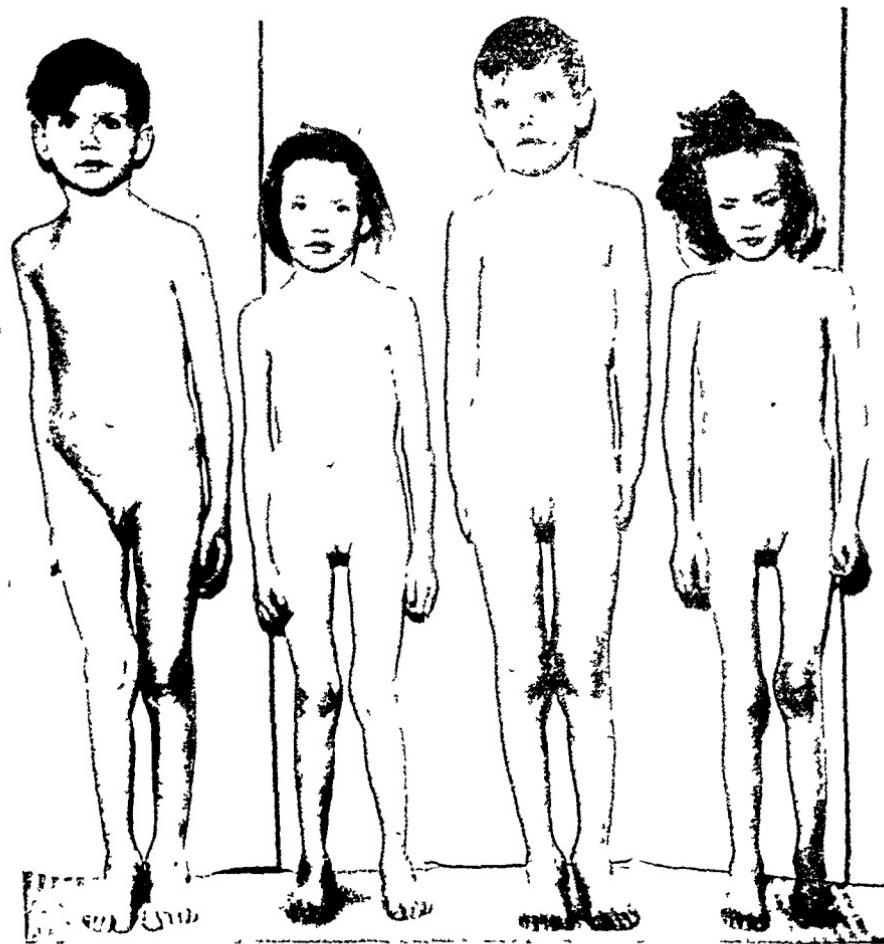


Fig. 2—Case 2, age 9, Case 1, age 9, Case 3, age 8, Case 4, age 7. Photograph was taken May 10, 1947.

Electrocardiographic Examination on April 17, 1947.—PQ was 0.19 sec; QRS 0.09 sec.; T_{1-2} +; QT 0.38 sec. (upper normal limit 0.374 sec.). On June 17, 1947, PQ was 0.18 sec.; QRS 0.12 sec.; T_{1-2} +; QT 0.40 sec. (upper normal limit 0.38 sec.). (See Fig. 3.) On Sept. 26, 1947, electrocardiogram was normal. Otherwise nothing pathologic was found. Wassermann test was negative. Normal figures for serum calcium, serum phosphorus, serum iron, serum proteins, and cholesterol were obtained.

He received the same treatment as given his sister without any definite effects.

In June, 1948, the skin was as before. There was further diminution of hearing. He was deaf on the right side; whispering ad concham and speech half a meter away were audible on the left side. There was slight night blindness. A moderate degree of horizontal rotatory nystagmus on looking to both sides was noted. Fundi were as before. Vision was 5/5.

Gait was slightly ataxic. Slight dysdiadochokineses and intention tremor of both arms were present, along with slight atrophy of the tibialis anticus group of muscles on both sides. Deep reflexes were weak as before. She was discharged to her home.

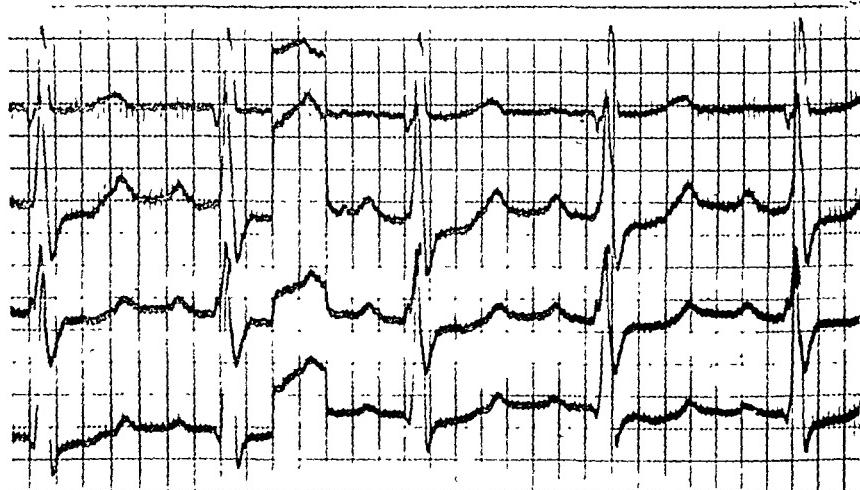


Fig. 3.—Case 3. Electrocardiogram taken June 17, 1947. Heart rate was 83; PQ, 0.18 sec.; QRS, 0.12 sec.; T₁, T₂, T₃, and T₄ were plus; QT, 0.40 sec. The whole electric systole is too long. According to Ashman and Hull the upper limit of the normal PQ interval in children 7 to 13 years of age with heart rate of 71 to 90 is 0.17 sec.

QRS of 0.12 sec. is definitely too long and the upper limit of normal QT for that cycle length is 0.37 sec. (according to Ashman and Hull).

CASE 3.—A boy, an only child, born on Sept. 24, 1939, was healthy till the autumn of 1946, when his skin began to be dry, desquamating, and itching. Anorexia and lassitude were present and walking was poor.

On admission on April 22, 1947, he was thin. His I.Q. was 86.4. His skin was dry and desquamating everywhere. Slight diminution of hearing of ill-defined type was observed on both sides. Fundi and field of vision were normal. Vision was 5/5 on both sides.

Neurological Examination.—General atrophy of the muscles was most marked distally, with corresponding pareses. Absence of the deep reflexes of arms and legs and slight ataxia of the arms were observed. There was no increase of tenderness on deep pressure on the muscles. There was loss of the vibration sense distally in all limbs. The sense of position was uncertain. Hypoesthesia (possibly) was present on touch distally of the lower limbs. There was no thickening of the palpable nerves.

Electrocardiographic Examination.—PQ was about the upper limit of the normal.

As in the preceding cases, large doses of B vitamins were given and there was, perhaps, some improvement in his hearing and in the strength of his muscles. There was no return of the deep reflexes. After an attack of mumps he

became definitely worse, he could not walk as well as before, and the movements of his hands were less coordinated.

On readmission on April 12, 1948, the skin was as before, hyperkeratotic on the elbows. Definite diminution of hearing on both sides was noted. The fundi showed diffuse, atypical pigment changes such as are found in cases of tapetoretinal degeneration. There was night blindness. A neurologic examination showed deterioration. Dysmetria of the arms was quite plain. Gait was more ataxic and unsteady before, with steppage. Romberg's sign was present. Considerable atrophy and paresis of all the limbs were most marked distally.

Electrocardiographic Examination.—A rather long conduction time and T₁ flat were demonstrated.

In other respects the physical examination was negative. Wassermann test was negative. The figures for serum proteins, serum chlorides, serum calcium, serum phosphorus, serum phosphatase, and serum cholesterol were normal. Intelligence was as before.

CASE 4.—A girl whose parents were first cousins, was born on Aug. 2, 1939, and was well until she was 4 years old. Her disease began with dryness and desquamation of the skin. Anorexia and loss of weight were present. After the age of 5 years, difficulty in walking and running, and after the age of 6 years, definite impairment of hearing occurred.

On Dec. 2, 1946, she appeared small and thin; she seemed quite attentive, but her deafness interfered with tests of her intelligence.

The skin everywhere was dry and desquamating, with abnormal furrows. The scales from her skin were large and some were brown.

Bilateral deafness was present.

The fundus was light-colored, with long intervals between the choroid vessels. Some clumps of pigment were spread over the fundus.

Neurological Examination.—General atrophy of the muscles and loss of the deep reflexes in arms and legs were noted. She was ataxic with unsteady gait. Romberg's sign was present. Coordination and sensation were difficult to investigate.

Electrocardiographic Examination.—The QRS complex was splintered. QT was about the upper limit of the normal (see Fig. 4).

In other respects the physical examination showed normal conditions. Wassermann was negative. Various blood tests gave normal values.

On May 6, 1947, the fundi showed incipient tapetoretinal degeneration. In other respects there was no change.

Treatment with B vitamins yielded no appreciable effects. In the autumn of 1947 she became steadily worse and was finally bedridden. The condition of her skin, "alligator skin," became worse, and she lost much weight. (See Fig. 5.) Her parents exerted themselves to provide her with an adequate and nutritious dietary, and during the winter of 1948 her weight rose by 10 kg. Her arms and legs became gradually a little stronger, and her skin showed marked improvement. Words she had not used for more than a year came back to her. In the spring of 1948 she could sit up in a chair and play. She remembered all the words she had learned before she became deaf, but there was no improvement in her deafness. Apparently she developed night blindness, for her father remarked of his own accord that she saw badly in the dark, not noticing that her parents had entered the room when it was dusk.

On May 22, 1948, she appeared well nourished, and her skin was normal, the ichthyotic changes having disappeared. She was stone deaf, not reacting



Fig. 4.—Case 1. Electrocardiogram Dec. 17, 1946. Heart rate was 115. PQ was 0.16 sec., QRS, 0.06 sec., T₁, T₂, T₃, and T₄, plus. QT was 0.32 sec.

The most striking features here are the abnormally notched QRS complexes in Leads II and III and the fact that the QT interval lies at the upper limit of normal. (Ashman and Hull's tables.)



Fig. 5.—Case 4. Ichthyosis. Photograph taken May 10, 1947.

to loud sounds. An examination of the eyes showed considerable vertical-rotatory nystagmus which prevented a close examination of the fundi. The muscles of her limbs were weak, and there was marked ataxia. There was a striking change since the last examination in her deep reflexes, which were now plainly present, the patellar reflexes being even brisk.

Electrocardiographic Examination.—The QT distance was above the upper normal limit.

Intelligence was as before.

In all four cases, there was a marked increase in total proteins in the cerebrospinal fluid, whose cell count was normal. The findings are given in the following table:*

TABLE I. SPINAL FLUID FINDINGS IN CASES 1 TO 4

PATIENT NO.	I	II	III	IV					
Date	20/3 1947	16/9 1947	24/4 1947	4/6 1947	4/6 1947	24/10 1947	14/4 1948	4/12 1946	24/5 1948
No. of cells	7/3	8/3	4/3	4/3	1/3	5/3	23/3	3/3	3/3
Positive total pro- teins	1/100	1/460	1/50	1/100	1/30	1/55	1/100	1/100	1/90
Positive globulin	1/5	1/16		1/5	1/2	1/2	1/3	1/4	1/5

DISCUSSION

Here we are most probably dealing with a familial disease exhibiting a recessive mode of hereditary transmission. It began between the ages of 4 and 7 years with anorexia, an unsteady gait, skin changes suggestive of ichthyosis, and progressive diminution of hearing of the neurogenic type. An examination showed slight pigment changes in the retina, night blindness, ataxia, and other cerebellar manifestations and a polyneuritis-like condition with loss of the deep reflexes. (In Case 4, the reflexes did, however, return after an observation period of a year and one-half.) The cerebrospinal fluid showed albumino-cytological dissociation with a normal cell count and marked increase of proteins. The electrocardiograms were pathologic. While under observation the children showed no definite diminution of intelligence.

The polyneuritis-like manifestations, the changes in the skin, and the diminution of hearing were suggestive of avitaminosis B. At variance with this diagnosis were the retinitis pigmentosa, the cerebrospinal fluid findings, and the lack of response to the energetic administration of B vitamins.

The so-called juvenile form of amaurotic idiocy is characterized by retinitis pigmentosa and it may, like the late infantile form, run a course with cerebellar-ataxic manifestations figuring prominently. In conflict with this diagnosis in our cases was the absence of diminution of vision, of progressive dementia, and of extrapyramidal manifestations. As far as we know, descriptions of this disease have not included a marked increase in the quantity of proteins in the cerebrospinal fluid nor the electrocardiographic changes observed in our patients.

*The total proteins in the cerebrospinal fluid are determined by Bisgaard's dilution method (Heller's nitric acid stratum test). Normally the test should become negative at a dilution of 1 to 15 or less. A dilution of 1/100 + corresponds to a total protein content of 165 mg. per cent. The globulin content is determined by Bisgaard's dilution method with a saturated solution of ammonium sulphate as reagent. Normally the globulin reaction disappears at a dilution of 1 in 2 if it is at all present.

The clinical picture presented a certain similarity to the hereditary ataxias. In particular one is tempted to think of an atypical form of Friedreich's disease in this connection. In our cases, however, we lack manifestations which, without being essential to the diagnosis of this disease, are very characteristic of it; namely, dysarthria and skeletal deformities (deformities of the spine, Friedreich's foot). Our patients also presented several manifestations such as retinitis pigmentosa with night blindness, the polyneuritis-like picture, and the considerable hyperalbuminosis in the cerebrospinal fluid—features which are not, as a rule, found in Friedreich's disease.

On the other hand, the above-mentioned findings in our cases are characteristic of a familial syndrome, heredopathia atactica polyneuritiformis, described in 1945 and 1946 in adults by one of us (S. R.). This syndrome was observed in five patients* whose ages ranged from 20 to 30 years and a little over. They belonged to two Norwegian families with no blood ties between them. This syndrome is characterized by the following features: atypical retinitis pigmentosa with night blindness and concentric limitation of the field of vision, a chronic polyneuritis-like picture with progressive pareses of the limbs distally, ataxia and other cerebellar manifestations, considerable increase of the protein content of the cerebrospinal fluid without an increase in the number of its cells, and also, in some cases, diminution of hearing of a neurogenic type and electrocardiographic changes. The parents of these patients were, in every case, blood relations. It is probable that this syndrome depends on a single recessive gene, not sex linked.

From the account just given there would seem to be a striking resemblance in the clinical picture presented by our patients to that of heredopathia atactica polyneuritiformis. The resemblance is so close that we are driven to the conclusion that these children suffered from this syndrome which has hitherto not been described in childhood.

The ichthyosis-like skin changes were striking in all these children. Similar ichthyotic changes were plainly present in one of the adult cases of heredopathia atactica polyneuritiformis described by Refsum. Since the appearance of Refsum's original publication it has been learned that another patient in the same family was subject to similar skin changes. Among the other adult patients there were, however, no such changes.

It is not yet quite clear what is the nosological position of heredopathia atactica polyneuritiformis. Is it an independent nosological entity, or does the syndrome belong to the heredo-ataxias or to the cerebral lipidoses, to be grouped with amaurotic idiocy and Niemann-Pick's disease? In the case of Case 1, a neurohistologic examination yielded the following main points mentioned in a preliminary report by Dr. Jan Cammermeyer:

Fibrous thickening of the leptomeninges with fat macrophages. A moderate degree of degeneration of the peripheral nerves. Changes in the anterior horn cells in the spinal cord. Homo- and contralateral degeneration of the olivocerebellar tracts. Marchi positive fat in moderate quantities in nerve cells and ependyma.

*A sixth case, observed in one of the families of these patients, has subsequently been discovered.

There was no sign of inflammatory changes, of toxoplasmosis, nor of torulosis.

The histologic investigation of the postmortem material presented by the adult patients suffering from heredopathia atactica polyneuritiformis reported on in Refsum's original publication has not yet been completed. It can, however, already be stated that, according to Dr. Cammermeyer, the neurohistologic changes presented by these two patients corresponded in their principal features to the above-mentioned findings in Case 1. The localization and intensity of these changes varied, however, from case to case. In the case of a third adult patient, examined post mortem, changes reminiscent of interstitial hypertrophic neuritis were found in all the nerves examined.

SUMMARY

An account is given of four children, three of whom were born in consanguineous marriage. Their disease began between the ages of 4 and 7 years, and it showed a slowly progressive development with the following features: diminution of hearing of neurogenic origin amounting to complete deafness in some cases; atypical retinitis pigmentosa with night blindness; ichthyosis-like skin changes; ataxia and other cerebellar manifestations; polyneuritis-like manifestations with weakening or loss of the deep reflexes; a considerable increase in the protein content of the cerebrospinal fluid without any increased cell count and electrocardiographic changes. The intelligence was not diminished.

A brief summary of the neurohistologic findings is given.

The disease is considered to be identical with the heredopathia atactica polyneuritiformis described by S. Refsum in adults. Hitherto a description of this disease in children has not been given.

REFERENCES

- Cammermeyer, Jan: Om de anatomiske funn i to tilfelle av dr. S. Refsum's materiale av "et tidligere ikke beskrevet (?) familiert syndrom," Communication at the IX Congress of Scandinavian Neurologists 1945, Nord. Med. 29: 617-618, 1946.
 Refsum, Sigvald: Heredoataxia hemeralopica polyneuritiformis*—et tidligere ikke beskrevet familiert syndrom? En foreløpig meddelelse (English summary, Heredoataxia Hemeralopica Polyneuritiformis: A Familial Syndrome Not Previously Described? Preliminary report), Nord. Med. 28: 2682-2686, 1945.
 Refsum, Sigvald: Et tidligere ikke beskrevet (?) familiert syndrom: "heredo-ataxia hemeralopica polyneuritiformis," (Report on IX Congress of Scandinavian Neurologists, September, 1945), Nord. Med. 29: 617-618, 1946.
 Refsum, Sigvald: Heredopathia Atactica Polyneuritiformis: A Familial Syndrome Not Hitherto Described, Oslo, 1946, Johan Grundt Tanum, pp. 303. Also printed in Acta Psychiat. et neurol., 1946, Supplementum XXXVIII.
 Salomousen, Leif, and Skatvedt, Marit: Four Cases of Heredopathia Atactica Polyneuritiformis: Report on IX Northern Pediatric Congress, August, 1948, Acta Paediat. (in Press).

*This term gave a good indication of the of this syndrome. But there is no anatomical proof of its relationship We have, therefore, given preference to the more neutral term, her neuritiformis.

^tA review of this monograph has been given in New England J. Med. 236: 996, 1947. Refsum's Disease (Editorial by H. R. Viets).

ADRENOCORTICAL INSUFFICIENCY IN INFANTS WITH THE ADRENOGENITAL SYNDROME

A CLINICAL AND PATHOLOGIC STUDY OF FOUR CASES

WOLF W. ZUELZER, M.D., AND ALEXANDER BLUM, JR., M.D.
DETROIT, MICH.

IT IS evident from a review of the literature that the adrenogenital syndrome is compatible with normal or even increased function of the adrenal gland as regards the metabolism of salt, water, carbohydrates, and nitrogen. The work of Young,¹ the monographs of Broster and Vines,² and the review article by Haymaker and Anderson⁴ fail to mention the occurrence of adrenal insufficiency in patients with the adrenogenital syndrome. Numerous cases of adrenal virilism have been described in which the patients attained a normal life span or were subjected without mishap to major surgical operations.^{1, 2, 3} A few reports, however, found chiefly in the pediatric literature, indicate that, in children at least, the masculinizing effects of adrenal cortical hyperplasia may be accompanied by serious impairment of the metabolic functions of the adrenal cortex. In such patients the clinical picture has been characterized by dehydration, vomiting, diarrhea, sometimes brownish pigmentation of the skin, and a tendency toward sudden circulatory collapse suggestive of a destructive lesion in the adrenal glands as in Addison's disease rather than the hyperplasia which was actually found at autopsy.

The combination of cortical insufficiency, masculinization, and diffuse adrenal hyperplasia forms a distinct anatomic-physiologic entity. Although we were able to find only seventeen cases of this type in the literature,⁵⁻¹³ our experience suggests that the syndrome is more common than this figure would seem to indicate. We have observed four instances in 1,068 autopsies of children from birth to 13 years of age over a period of six years, an incidence of 0.37 per cent. There were 770 infants under one year in the group, and since all the patients to be reported were less than a year old, the incidence in this age group was 0.52 per cent. Our observations, though far from complete, are presented in order to direct attention to the clinical, biochemical, and pathologic problems connected with this syndrome.

CASE REPORTS

CASE 1.—Γ. M., a white infant presumed to be of female sex, entered the hospital at the age of 2 weeks because of vomiting, thrush, and an ear infection. The vomiting had begun on the ninth day of life and occurred shortly after meals. She weighed 5 pounds, 9 ounces, having lost 1½ pounds since birth. The prenatal and neonatal histories were noncontributory.

Physical examination revealed slight redness of the external canal of the right ear. The gums had been painted with Gentian violet. The only other abnormality concerned

Children's Hospital of Michigan and the Departments of Pediatrics and Pathology, Wayne University College of Medicine.

the external genitalia. The clitoris was hypertrophied and grooved on its inferior surface, thus resembling a penis with hypospadias. The groove led to a single opening which appeared to represent both urethral and vaginal orifices. The labia minora could not be seen. The labia majora were present and somewhat resembled the halves of a scrotum with thick, wrinkled skin but without a raphe or palpable testes.

Laboratory Data.—Except for the constant presence of a trace of albumin, the urine was found normal on numerous occasions. The hemoglobin was 18.5 Gm. per 100 c.c. on admission and gradually fell to 12.3 Gm. during a period of two months. The white blood count was 12,200 on admission and 13,000 three weeks later. The Kline test for syphilis was negative. The nonprotein nitrogen on one occasion was 89.1 mg. per cent and on another 41 mg. per cent. The fasting blood sugar five weeks after admission was 60.8 mg. per cent ("true sugar" determination).¹⁴ Following the injection of 4.5 Gm. of glucose it rose to 191 mg. per cent in one hour.

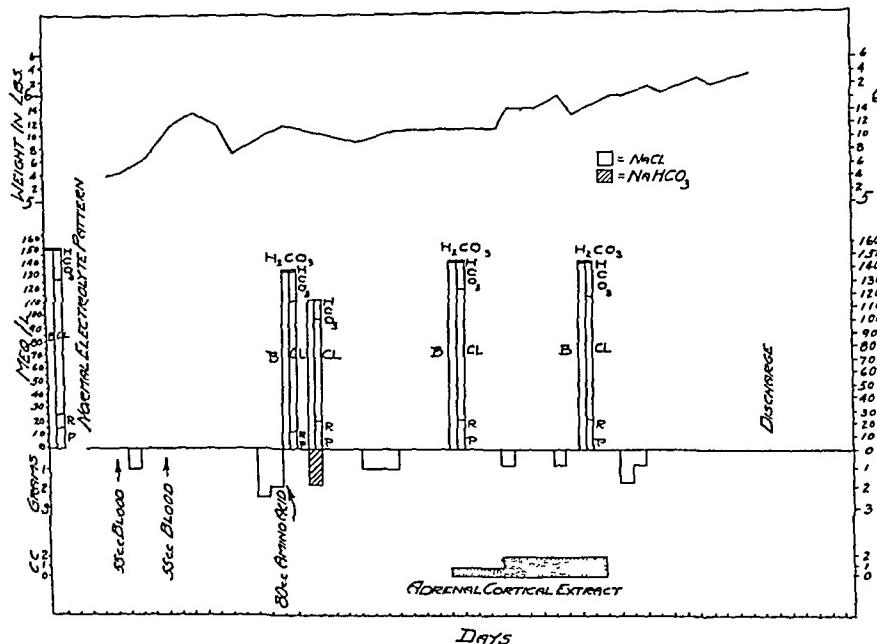


Fig. 1.—Graphic presentation of biochemical data in Case 1. The plasma electrolyte pattern is shown above the line with the normal values given on the left for comparison. The boxes below the line indicate the amount in grams of sodium chloride and sodium bicarbonate given.

The plasma electrolyte structure of this patient was investigated on four occasions. The results are shown graphically in Fig. 1. It will be seen that the total plasma base was consistently lower than normal and that the values for chlorides roughly paralleled those for total base.

Course.—The patient remained in the hospital for two months. During this period she vomited at times, but rarely enough to account for the marked delay in weight gain. Her appetite was usually good. There was a tendency to constipation. Barium studies revealed no pathologic changes in the gastrointestinal tract by x-ray. An intravenous pyelogram was attempted but the dye was not visualized in the urinary tract.

Although the feedings were frequently supplemented by parenteral injections of glucose solution, normal salt solution, plasma, and whole blood, the infant always appeared clinically dehydrated and gained only 12 ounces in over two months. The administration of adrenal cortical extract in amounts of 1 c.c. ($2\frac{1}{2}$ rat units per cubic centimeter) was without appreciable effect.

Following discharge from the hospital her condition remained unchanged for another two months. She then had a bout of severe vomiting and was readmitted. Her weight at this time at the age of 4½ months was 6 pounds, 15 ounces, exactly what she had weighed at birth. The temperature was 98.6° F. She appeared quiet, rather feeble, dehydrated, but by no means critically ill. Careful examination revealed no abnormal findings in the heart or respiratory tract. Three hours after admission the patient suddenly expired.



Fig. 2.—Semidiagrammatic drawing illustrating the appearance of the internal and external genitalia in Case 1.



Fig. 3.—Photograph of adrenals, Case 1.

Autopsy Findings.—A complete autopsy was performed within seventeen hours after death. The body was that of a poorly nourished female hermaphrodite infant measuring 55 cm. in length. Skin and mucous membranes were dry and somewhat pale. The external genitalia were as described clinically. The clitoris measured 1.5 cm. and had a well-developed prepuce. The single orifice in the region of the vestibule led into a tubular

structure which proved to be the common outlet of urethra and vagina. Three millimeters from the external opening there was a shallow valvelike fold partially covering the entrance into a narrow tubular vagina measuring only 3 mm. in length and merging gradually with an elongated, cigar-shaped uterus which lacked a distinct cervix and which measured 2.5 cm. in length. The Fallopian tubes were well developed. An ovary was present on each side. The right measured 2.0 by 0.6 by 0.3 cm., the left 1.3 by 0.5 by 0.2 cm. Both appeared grossly normal. Anteriorly the common outlet was continuous with the urethra, which presented no further abnormalities.

The adrenals were markedly enlarged, having a combined weight of 14 grams. They were of the usual shape, rather firm, muddy yellow-gray in color. The external surfaces showed a marked pattern of convolutions. On cut surface the yellowish cortex measured 1 mm. in width on the average and seemed well demarcated from the softer, reddish-brown medulla.

The thymus extended to the level of the third rib, measured 3 cm. in width, and weighed 9 grams. The spleen weighed only 7 grams. The pancreas was not unusual in size and appearance. The kidneys weighed 15 and 14 grams. The liver was of the usual size and weight. The heart was underweight, but the right ventricle was dilated. Examination of the brain revealed a slight atrophy of the left frontal and parietal lobe but no reduction in the weight of the organ as a whole. No gross abnormalities could be demonstrated in the pituitary gland or the pineal body.

The adrenals were fixed in Zenker's fluid, Zenker-formol, Helly's, Muller's, and Orth's fluid, formaldehyde and absolute alcohol. Appropriate paraffin sections were stained with hematoxylin-eosin, Mallory's aniline blue, and Fujiwara's modification¹⁵ of Broster and Vines' stain for androgenic cells. Frozen sections were stained with Scharlach-R and Nile blue sulfate.

On microscopic examination it was evident that the enlargement of the adrenals was due to hyperplasia of the cortex. The width of this layer was greatly increased, partly as the result of an elongation of the cell cords of the zona fasciculata, partly because of accumulations of epithelial cell masses beneath and within the capsule, as well as on the surface, producing irregular elevations and convolutions. A true zona glomerulosa could not be distinguished. In some areas the slightly blunted ends of the columns arising from the zona fasciculata abutted directly on the capsule. In most places, however, the columns spread out and changed direction, merging into a layer of variable thickness where the cells were arranged in strands and sheets parallel to the surface. Frequently such strands penetrated between the collagen fibers of the capsule which appeared to have stretched and split in these areas. Larger masses of epithelial cells had mushroomed through the capsule and formed adenoma-like nodules and excrescences which, as a rule, were fused at their base to the main body of the cortex but in some instances appeared as separate structures. Similar masses and areas of irregular thickening of the cortex proper were observed in the depth of the tissue where infolding had removed the cortex from the surface.

The "adenomas" sometimes lacked complete capsules but diffuse infiltration of the adjacent tissues was never seen and the tissue appeared hyperplastic rather than neoplastic throughout.

The inner border of the zona fasciculata was not sharply defined but merged into an indistinct, narrow, zona reticularis. The latter was demarcated toward the center of the gland by a fairly broad, fibrous, boundary zone in which scattered single degenerating epithelial cells were found. The core of each adrenal was formed by ample amounts of typical chromaffin tissue.

There was distinct variation in the appearance of the epithelial elements composing the cortex. Most of the cells in the zona fasciculata were of the usual size. Their cytoplasm often was pale, finely honeycombed, and contained small globules of fat which stained a bright red with Scharlach-R. This reaction was demonstrable almost exclusively in the zona fasciculata and produced a broad, irregular, spotty band of red midway between



Fig. 4.—Low-power view of the adrenal. Note masses of cortical tissue penetrating the capsule.

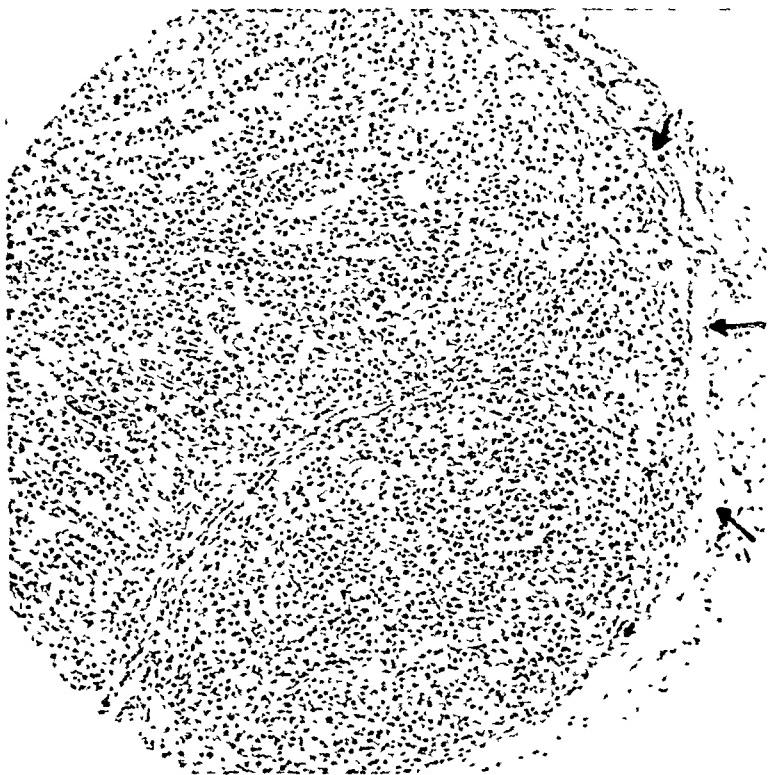


Fig. 5.—High magnification showing absence of glomerulosa and presence of epithelial cells mushrooming through the capsule.

the inner and outer borders of that zone. Many cells throughout this layer had a homogeneous or finely granular cytoplasm which took the eosin stain more evenly than the honeycomb cells. Single cells or small groups of cells here and there had a shrunken appearance with deeply staining, homogenized cytoplasm and pyknotic nuclei suggesting necrobiosis. Still others had spongy, swollen bodies and lacked demonstrable nuclei.

Toward the periphery of the zona fasciculata the character of the epithelium began to change. There was an admixture of cells slightly larger than those composing the middle portions and characterized by an abundant granular eosinophilic cytoplasm. Such cells were even more frequent in the layer of cells beneath and within the capsule and predominated in the nodular projections on the surface. The resemblance of these elements to cells of the so-called fetal cortex was often striking. However, even small rows and nests of epithelium in these regions were seldom uniform in composition but contained smaller cells indistinguishable from those found in the deeper layers of the zona fasciculata and also cells with honeycombed cytoplasm. The occurrence of morphologic transitions between the various cell types made the distinction between cells of "fetal cortex type" and "permanent cortex type" uncertain and impractical. The cells of the subcapsular area showed little or no sudanophilia.

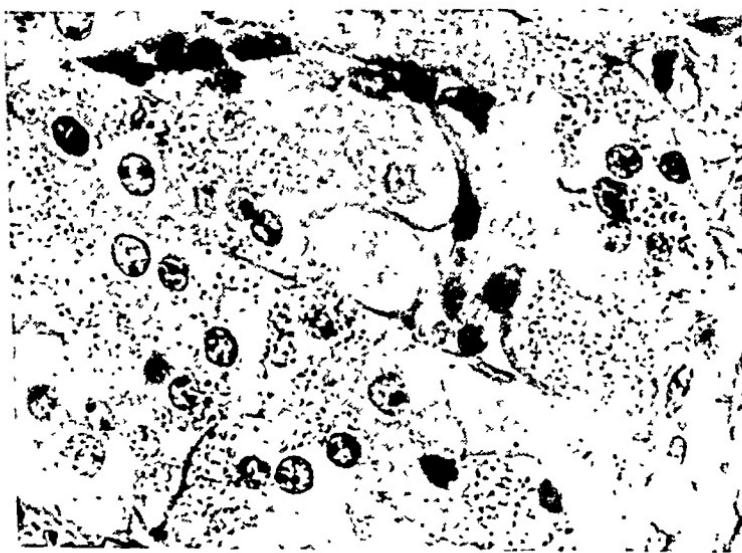


Fig. 6.—High-power view of outermost cortex showing presence of numerous cells filled with fuchsinophil (black) granules.

Fuchsinophil granules were occasionally seen in the cells of the outer zona fasciculata and even more frequently in the cell masses beneath and beyond the capsule. These granules were seen most easily in sections stained with Mallory's aniline blue after fixation in Helly's fluid. Although they were also demonstrable with Fujiwara's modification of the method developed by Broster and Vines, this stain proved far less satisfactory, partly because of the lack of contrast which Mallory's stain provided. With the latter technique the granules appeared as bright, cherry red, evenly distributed structures of uniform size against a light buff-colored, gray, or sometimes clear, colorless, background of cytoplasm. Occasionally the granules were more orange or even yellowish in color. In general the cells containing fuchsinophil granules corresponded to the larger, granular cells with eosinophilic cytoplasm resembling fetal cortex cells, but smaller and paler cells occasionally also contained such granules and rarely they could be demonstrated in cells with spongy, honeycombed cytoplasm.

Examination of the gonads revealed no appreciable deviation from the structure of the average infantile ovary. The cortex was densely crowded with primary follicles and the deeper layers contained Graafian follicles in various stages of development, small cyst formations, and atretic follicles.

The pituitary contained a mixture of chromophobe and chromophil cells with a slight possible increase in the number of basophile elements as compared with control sections from other infants in the same age group as the patient. It seemed doubtful, however, that this increase would have been noticed on a routine examination of the gland.

The remaining endocrine organs did not appear remarkable except for the lack of involutionary changes in the thymus which deserves mention in the presence of general emaciation and atrophy of the adipose tissue. In this connection the presence of numerous small lymph follicles along the course of the small bronchi was of interest. These, like the tissue of Peyer's patches, had distinct secondary centers composed of large, "young" lymphocytes. The malpighian corpuscles of the spleen, on the other hand, lacked well-defined centers but appeared numerous, possibly because they were crowded together in the pulp which was quite poorly filled with erythrocytes.

Comment.—The salient clinical features of this case were unexplained vomiting, a degree of dehydration which seemed out of proportion to the amounts of fluid lost, nitrogen retention, a lowering of the "total base" in the plasma, and a proportionate lowering of the plasma chlorides, persistent failure to gain weight, and finally a sudden, unexpected death. In addition, pseudohermaphroditism was present but there was no evidence of progressive changes in the genitalia.

Although a detailed analysis of the plasma cations was not carried out, it is evident that the lowering of the plasma base (Fig. 1) must have entailed a reduction in the sodium concentration. Unfortunately, potassium determinations were not done. The clinical and biochemical findings were compatible with the picture of adrenal insufficiency and, in fact, could hardly be explained on any other basis. The autopsy findings eliminated lesions in the kidneys or the intestinal tract as possible causes for the metabolic disturbance and confirmed the clinical suspicion of pathologic changes in the adrenals. Since these organs showed hyperplasia rather than destruction or atrophy, it must be assumed that the cells produced salt and water hormone either in inadequate amounts or not at all, unless one wishes to postulate the secretion of substances counteracting the effects of these hormones. The apparent failure of substitution therapy may be ascribed to inadequate dosage of cortical extract administered to this patient and, therefore, does not lend itself to any conclusion.

The histologic findings were suggestive of the presence of fetal cortex, but it is clear from the description that a substantial amount of tissue indistinguishable from the ordinary postnatal adrenal cortex was present. In any event the function of the normal fetal cortex is at present unknown. The demonstration of fuchsinophil granules was considered diagnostic for androgenic cells by Broster and Vines¹ and others,¹⁶ but this criterion has not been generally accepted.⁸ Its specificity is doubtful, yet the combination of this finding with the other features of the case may be significant. Correlation of functional disturbances with the morphologic evidence presented permits the conclusion that abnormal function of the hyperplastic adrenals was the basis of the clinical manifestations.

CASE 2.—S. S., a 20-week-old white infant, was admitted because of vomiting, diarrhea, malnutrition, and cough. The symptoms had begun at the age of one month with a paroxysmal cough accompanied by cyanosis, followed by vomiting of yellowish material. The mother described the illness as whooping cough. Diarrhea had accompanied the symptoms for the first two weeks but had since subsided. In spite of an excellent appetite the patient had lost considerable weight since the onset of "his" illness, weighing 2 pounds below the birth weight of 8½ pounds.

The child was born at full term and the delivery had been normal. The attending obstetrician and the family considered the baby to be a boy. The mother was 42 years old and had had an uneventful pregnancy. She had had eight previous children, seven of whom were in good health. Their sexes were not stated. One child had died at the age of 6 weeks from "diarrhea and malnutrition." This child had an abnormality of the external genitalia. He was described as having had a penis but no scrotum and had been considered a boy.

The patient was a lethargic, poorly nourished infant in a state of obvious severe dehydration. The weight was 5 pounds, 6 ounces. The skin was cold to touch and the respirations were shallow and irregular with frequent periods of prolonged apnea. The temperature was 97.4° F. The liver was palpable 2 fingerbreadths below the costal margin. There were moist, oozing granulations on the umbilicus.

The external genitalia were almost identical in appearance with those described in Case 1. The identification of this patient's sex was even more difficult, however, because the large, corrugated folds resembling scrotum but lacking testicles were fused toward the perineum in a median raphe.

Laboratory Data.—The urine was acid and contained sugar (2 plus) after parenteral administration of glucose but was otherwise normal on several occasions. There was a mild anemia, the hemoglobin being 9.6 Gm. and the red blood count 2,960,000 per cubic millimeter. The white blood count was 12,400 with a differential count of 77 per cent neutrophils, 22 per cent lymphocytes, 1 per cent eosinophils. The Mazzini flocculation test was negative. The nonprotein nitrogen of the blood was 42.6 mg. per cent, the blood sugar 65 mg. per cent. The results of plasma electrolyte studies are shown in Fig. 7 and will be described in connection with the therapy given.

Roentgenograms revealed questionable pulmonary emphysema. The heart and the skeletal structures appeared normal.

Course.—The patient received intravenous infusions of one-seventh molar sodium lactate, normal salt solution, and plasma. Notwithstanding this therapy, the total plasma base on the third hospital day was only 137 meq. per liter, chlorides 92.0 meq. per liter, carbon dioxide 16.7 meq. per liter. The so-called "R-fraction" was slightly increased to 14.9 meq. per liter. Treatment with adrenal cortical extract was then begun in daily doses of 2 c.c. (5 rat units). The child was offered a mixture of Karo syrup and salt solution between feedings and additional saline parenterally. Sodium bicarbonate was also given by mouth. There was definite improvement for a period of ten days. The child ate well, was able to maintain a normal body temperature without external application of heat and to gain weight without further parenteral fluid therapy. The amounts of sodium given as chloride and bicarbonate salts were decreased and the adrenal cortical extract was increased to 10 rat units on the eighth hospital day when the total plasma base had risen to 146.5 meq. per liter. Two days later the child again appeared dehydrated and the plasma base had dropped to 104 meq. per liter. The following day diarrhea appeared and there was a precipitous loss of weight. The dosage of adrenal cortical extract was increased to 15 rat units daily. Because of apparent dehydration the patient received intravenous infusions of glucose and saline solutions totaling 675 c.c. and an equal amount of fluids by mouth. The total salt intake for that day was later computed to be 9.5 Gm. of sodium chloride and .666 Gm. of sodium bicarbonate.

On the day following this treatment the clinical condition of the patient indicated acidosis. Still sodium chloride was given on that day. In addition 2 Gm. of soda bicarbonate was administered intravenously as a 4 per cent solution in glucose. On the next

day, fifteen days after admission, the clinical signs of acidosis were slightly less marked. The diarrhea still continued, and the abdomen had become evenly distended. At this time the total plasma base was 191 meq. per liter. Simultaneously the chlorides had risen to 161.5 meq. per liter, while the carbon dioxide content had fallen to 4.6 meq. per liter. Before these results were known 2 mg. soda bicarbonate in glucose was again given intravenously and 100 c.c. of 85 per cent sodium chloride solution by hypodermoclysis. All sodium chloride administration was discontinued but more soda bicarbonate was given, together with glucose. In the afternoon the total base was still 169 meq. per liter. The chlorides had dropped to 138 meq. per liter and the carbon dioxide had risen slightly and was now 9.8 meq. per liter. By evening the child was moribund though the plasma electrolyte continued to approach more normal values. The last determination that night showed a total base of 165 meq. per liter, chlorides 130 meq. per liter and carbon dioxide 17.0 meq. per liter. The respirations became labored, the color was ashen, and the distention was increasing. The patient died early the following morning, the sixteenth hospital day. The biochemical findings are summarized in Fig. 7.

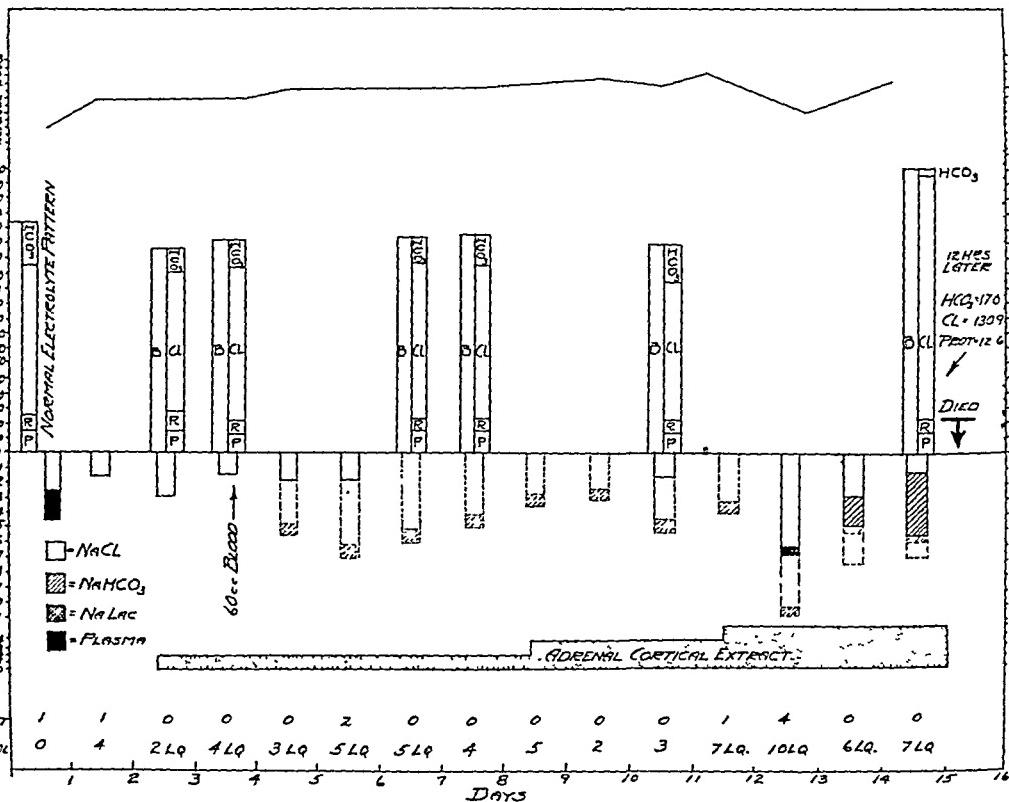


Fig. 7.—Graphic presentation of biochemical data in Case 2. Symbols are used in the same manner as in Case 1. The solid parts of the blocks below the base line indicate electrolytes given parenterally. Broken lines indicate oral electrolyte intake.

A complete autopsy was performed three hours after death. The clinical diagnosis of adrenal cortical hyperplasia was confirmed. The adrenals had a combined weight of 17 Gm, and were in every respect similar to those described in Case 1. The genitalia shown in Fig. 8 were also virtually identical with those in the previous patient. The only difference was the presence of a well-formed uterine cervix projecting into the vagina. The

opening of the latter into the common urogenital sinus was marked by a moundlike elevation. The ovaries measured 1.8 by 0.8 by 0.4 and 1.8 by 0.5 by 0.1, respectively.

In contrast to Case 1 the thymus weighed only 2 Gm. The spleen, on the other hand, had a weight of 12 Gm., which must be considered within normal limits. The kidneys were slightly decreased in weight. The intestinal tract was not unusual except for rather marked distention of the small intestine. The right lung showed an area of pneumonic consolidation in the upper lobe.



Fig. 8.—External genitalia, Case 2.

Microscopic examination of the adrenals revealed a picture identical in every detail with that described in Case 1. Fuchsinophil granules were readily demonstrated in the outer layers of the zona fasciculata, in the cell layers parallel to the surface, and in the adenomas and projecting cell masses mushrooming through the capsule. A vastly larger number of cells in these areas were found to contain fuchsinophil cells than in Case 1 but the cells in the inner portion of the zona fasciculata and in the poorly developed zona reticularis were always free of such fuchsinophil granules, as were the single degenerating cells in the "boundary zone." Stainable lipids were absent throughout the cortex.

The pituitary showed a distinct increase in basophil cells which were approximately equal in number to oxyphil elements. No adenoma formation was observed. The remaining endocrine organs were not unusual.

The lymphoid tissues throughout showed depletion of lymphocytes and atrophy of the follicles.

Rather severe hydropic and degenerative changes were present in the epithelial cells of the proximal convoluted tubules of the kidney. The lumens of the collecting tubules were often filled with colloidlike casts.

The pulmonary alveoli were filled with a loose, inflammatory exudate without characteristic distribution. Mild infiltrations with polymorphonuclear leucocytes were present in the lamina propria of the large intestine.

Comment.—In this case the familial occurrence of the condition was of interest. The similarity both in regard to clinical and pathologic findings between this case and the preceding one is obvious. Again dehydration without apparent cause, lowering of the plasma electrolyte concentrations, and an

anomaly of the external genitalia were the outstanding clinical features. In addition this patient had a mild anemia and a history of respiratory infection.

The results of treatment in this case require further discussion. The administration of adrenal cortical extract in increasing dosage, combined with supplementary intake of sodium chloride and sodium bicarbonate in decreasing dosage, was distinctly beneficial. The clinical condition of the patient improved and the rise in the plasma electrolyte concentrations, notably the total base and chlorides, reflected this improvement.

It is not clear from the available facts why the plasma electrolytes subsequently failed to reach normal values in the face of combined hormone and salt therapy. Inadequate dosage of either or both agents must be considered as a possible reason. Whether the occurrence of diarrheal disease and the accompanying deterioration in the patient's general condition were indications of improperly regulated therapy or constituted signs of a complicating infection is likewise a matter for speculation. The presence at that time of infectious diarrheal disease of truly epidemic proportions in the hospital wards is in favor of the latter assumption.

The tremendous elevation of the plasma base and chloride values during the final phase seems clearly related to the injudicious use of saline infusions. The patient at that time was treated as if she had only diarrheal disease and acute dehydration with disregard of the presumptive adrenal insufficiency and the fact that adrenal cortical extract was being given.

The chemical data presented leave little doubt that a severe chloride acidosis developed. This was not surprising in view of the known inability of patients with adrenal insufficiency to retain sodium, while there is no interference with chloride retention. Hampton and Keplor¹⁷ have pointed out the danger of low potassium and high chloride intake to patients with adrenal insufficiency under treatment with cortical hormones.

The pathologic findings were almost identical with those in Case 1. The main difference was the involution of the thymus in Case 2, probably related to the clinical history of prolonged respiratory infection and diarrheal disease. The bronchopneumonia found at autopsy evidently represented a late complication.

CASE 3.—F. S., a white infant 7 months of age, allegedly male, was admitted because of failure to gain weight. The neonatal period had been uneventful. Injections for undescended testicles had been given for a period of ten weeks, starting when the infant was 3 weeks of age. There was no response to this therapy.

The birth weight had been 6 pounds, 11 ounces. Although the child always ate poorly the weight increased to 10 pounds, 12 ounces at the age of 3½ months. Thereafter the weight remained stationary in spite of many attempts to influence it by changes in formula. The child never took more than 2 ounces at a feeding and often vomited small amounts during meals. Solid foods were taken much better than milk. At the time of admission the weight was 10 pounds, 6 ounces. The patient was always constipated. Except for a slight cough two months prior to admission there had been no other symptoms.

The family history was of interest in that one of two siblings had died at the age of 4½ months with an "enlarged gland" in the abdomen. This child was said to have been unable to retain food. Its sex was not known.

Physical examination revealed a generalized brownish pigmentation of the skin. There was evidence of marked malnutrition. The genitalia were pseudohermaphroditic and identical in appearance with those of the two preceding patients. No other significant findings were recorded.

Before death only the following laboratory data were obtained: The hemoglobin was 12.9 Gm. The white blood count was 41,500 per cubic millimeter, the differential count yielded 19 per cent neutrophils, 73 per cent lymphocytes, and 2 per cent eosinophils. The Mazzini flocculation test was negative.

The patient appeared to be in fair condition and took feedings well in amounts of 3 ounces, but regurgitated the entire meal each time. Approximately twenty hours after admission he expired suddenly and without warning.

Heart's blood was taken for chemical studies one hour after death. The chloride was 102.5 meq. per liter, urea nitrogen 52.5 mg. per cent, sugar 0 mg. per cent, serum protein 7.18 Gm. per cent, hematocrit 14.5 vol. per cent.

A complete autopsy was performed three hours after death. The findings corresponded closely to those in the first two cases. Marked pigmentation of the skin was an additional feature and a pronounced linea nigra was noted over the lower abdomen. Heart and lungs appeared normal. No lesions were encountered in the intestinal tract. The spleen was small and weighed only 8.5 Gm. The thymus was large, measured 5 cm. in the transverse diameter, and weighed 19 Gm. The adrenals had a combined weight of 11 Gm. and had a muddy yellow color and nodular convoluted surfaces.

The genitalia consisted of a pair of ovaries of average size, a uterus with a well-developed cervix, and a vagina opening through a mound-shaped orifice into the urethra. The common outlet for urethra and vagina measured 1.6 cm. in length and ended beneath the enlarged clitoris. The kidneys weighed only 16 Gm. each.

Microscopic examination of the adrenals revealed again the picture of cortical hyperplasia with penetration of the capsule by cellular masses. Fuchsinophil granules were readily demonstrable in many of the cells near and on the surface of the glands and had the same distribution as in the preceding cases. Sudanophilic material in fine droplets was distributed unevenly throughout the cortical tissue, being most prominent in the outer and mid-fascicular area. There was more lipid in the subcapsular region than in Case 1. Lymphoid tissue, spleen, and thymus failed to show involutionary changes.

Comment.—This infant survived longer than the first two patients. This fact may be significant in regard to the development of abnormal pigmentation in the skin in this case. There was no information as to the time when this feature was first noted by the parents. Again there was a suggestive family history. The clinical features with which the parents were concerned consisted of failure to gain, vomiting, and constipation. The patient was being reared as a boy. The attempt to produce descent of testicles proves that the genitalia were malformed at birth and difficult to distinguish from true male organs. Death was again sudden and unexpected and seemed to be the result of circulatory collapse.

Chemical data unfortunately were lacking except for those obtained one hour after death. Only tentative conclusions can be drawn from these findings because of the "chloride shift" and other changes known to occur in post-mortem blood. The relatively high chloride level might be explained on this basis. The very high urea nitrogen, however, can hardly have been due to post-mortem changes alone. This finding may have been slightly exaggerated by post-mortem decomposition, but suggests strongly the presence of nitrogen retention during life and would be in keeping with adrenal insufficiency.

CASE 4.—E. T., a 4-week-old white male infant, was admitted because of refusal to nurse and weight loss. The child's birth had been uneventful and the birth weight was 6 pounds, 15 ounces. Although at first he had a lusty cry and healthy color, he soon appeared drowsy, nursed very slowly, and had a bluish color when he was discharged home on the ninth day of life. His weight was only 5 pounds, 10 ounces. He appeared weak and his skin was "hanging thin." A few days later the stools became watery and green and he began to vomit. His respirations were deep and his general condition seemed to deteriorate.

The family history was noncontributory. There were no siblings. The mother's pregnancy had been uneventful.

Physical examination showed an emaciated and severely dehydrated infant who appeared almost moribund. The heart rate was slow and the heart sounds were of poor quality. The respirations were deep and rapid. The skin had a waxy appearance. The left tympanic membrane was said to be bulging and a thick, gray exudate was present in the canal. The genitalia were those of a normally developed male infant. The remainder of the findings were noncontributory. The temperature was 98.8° F. The weight on admission was 5 pounds, 14 ounces.

The laboratory findings were limited to routine studies of blood and urine and furnished little information except for an elevated white blood count.

Course.—The patient received 110 c.c. of 10 per cent glucose solution in 0.85 per cent saline intravenously with dramatic improvement. The left eardrum was incised and pus was obtained. Following a transfusion of 55 c.c. of whole blood on the second day the child's condition seemed good. He took his formula hungrily, had no further diarrhea or vomiting, began to gain weight, and was discharged on the sixteenth hospital day. One week later he re-entered because of refusal to eat and rapidly developing listlessness during the last day. For two days prior to readmission he had had diarrhea. At this time the baby was in shocklike condition, limp, ashen gray, and dehydrated. The respirations were deep, labored, and irregular. The temperature was 98° F. A roentgenogram of the thorax showed consolidation in the right lower lung field. Urine was again not remarkable, the white blood count elevated, and a blood sugar was reported as 69 mg. per cent after intravenous glucose and oral feedings on the day of admission.

Again intravenous infusion brought dramatic relief, and for four days the patient did well. He then became feverish, vomited, refused feedings, and looked poorly. No new physical findings were elicited at this time. He expired the following morning.

At autopsy four hours after death bronchopneumonia was demonstrated and seemed sufficiently widespread to constitute in itself an adequate cause of death. There was a bilateral catarrhal otitis media. The adrenals were greatly enlarged, had a combined weight of 21 grams, and resembled those of the patients previously described. The penis and testicles were of appropriate size. The prostate appeared distinctly enlarged and measured 1.7 by 1.2 by 1 cm. The seminal vesicles did not seem large. The thymus weighed 5.5 grams. The spleen was small and weighed only 7.0 grams.

Microscopic studies revealed hyperplasia of the adrenal cortex. The changes were indistinguishable from those found in Cases 1 to 3 except for the absence of fuchsinophil granules. No tissue was preserved for Sudan studies. The glandular elements of the prostate were distinctly increased in size and number and often presented a corkscrewlike appearance. They were often filled with small amounts of finely granular eosinophilic material.

The seminiferous tubules of the testicles showed a definite increase in the number of spermatogonia as compared with control sections from normal infants. There was, however, no evidence of active spermatogenesis and no mitotic figures were found.

A slight increase in the number of basophil cells was thought to be present in the pituitary gland. No appreciable involutionary changes were noted in the thymus, spleen or lymphoid tissue.

Comment.—This patient, like those previously described, entered because of gastrointestinal symptoms, infection, and failure to gain weight. In this instance

the patient was a true male and no clue to the underlying condition could be determined from the external genitalia. At the age of 4 weeks there was no demonstrable precocity, although at autopsy an enlarged prostate was found. There was no clinical note of a digital examination of the rectum. Although this patient had an extensive bronchopneumonia, it is felt that this was merely a terminal complication and that there is as much reason to correlate the clinical picture with the changes in the adrenals as in the other cases. The dramatic improvement on both admissions after parenteral glucose and saline therapy is in keeping with this. As measured by weight the hyperplasia was even more marked than in the other cases, while gross and microscopic appearance of the cortical cells was identical except for the absence of fuchsinophilic material. There was no evidence of aberrant adrenal tissue being present in the testis.

DISCUSSION

Three of our patients were pseudohermaphrodites with female gonads and external genitalia resembling those of males with hypospadias and cryptorchidism. The fourth infant was a true male. The malformation of the genitalia in the females was typical of the congenital form of the adrenogenital syndrome in which excessive production of androgens by the fetal adrenals is thought to inhibit differentiation of female structures and to stimulate growth of the sex organs along male lines of development. The embryologic background of this malformation has been discussed in detail by Young² and others.^{1, 16, 18} The endocrine disturbance of early fetal life in females leads to fixed changes in the genitalia which are apparent at birth and therefore valuable in the diagnosis. Although the presence of pseudohermaphroditism does not in itself indicate persistence of active androgenic stimuli following the period of differentiation of the sex organs the development of patients surviving infancy is heterosexual and accelerated. The clinical signs of precocious maturity, however, do not, as a rule, appear for some time.

This point needs emphasis because in males the condition is usually recognized only after sufficient time has elapsed for the development of definite macrogenitosomia as illustrated by the case reports of Butler, Ross, and Talbot,⁶ and others.^{8, 10, 12} If the child dies in early infancy as did our male patient (Case 4) and those described by Dijkhuizen and Behr⁷ and others,^{11, 13} changes in the external genitalia cannot be expected.

The age factor was overlooked by Broster and Vines,¹ who cited briefly the case of an 8-week-old infant with bilateral hyperplasia of the adrenal cortex but failed to regard it as an instance of the adrenogenital syndrome because of the lack of changes in the sex organs.

The identity of the anatomic changes in the adrenals in both sexes, the similarity of the clinical picture, and the progression to macrogenitosomia in surviving male infants support the view that the underlying disorder is the same in both sexes. To our knowledge adrenal cortical hyperplasia has not been reported in otherwise normal female infants.

In two of our cases the family history was strongly suggestive of the same condition in a sibling. Among the cases reviewed by us there were four instances

of familial incidence among the offspring of fifteen mothers.^{7, 8, 10, 11} A positive family history thus constitutes an important diagnostic feature. In our cases the mothers, so far as known, had had normal pregnancies and showed no obvious signs of masculinization. No studies of maternal hormones seem to have been reported. The need for such studies is obvious.

The clinical features in our patients were compatible with a state of adrenal cortical insufficiency and similar to those described by other observers. Although there was little in this picture to differentiate it from ordinary diarrheal disease associated with enteric or parenteral infections in infants, the degree of dehydration often seemed out of proportion to the loss of fluid through diarrhea and vomiting. Evidence of infection, moreover, was either lacking or developed late in the course of the disease, indicating a complication.

Pigmentation of the skin so characteristic of Addison's disease in the adult was noted in only one of our patients. This feature was mentioned in four of the previously reported cases. It might be suspected that the appearance of pigmentation depended on the length of survival, for it was noted only in the oldest of our patients, but Butler, Ross, and Talbot⁶ described it in an infant 13 days of age while there was no pigmentation in the 6-year-old patient of Thelander and Cholffin.¹⁰

Chemical studies during life were reported in only three of the previously published cases. The most complete study was made by Darrow,¹² who reported low bicarbonate, chloride, and sodium values, elevated potassium concentration, and normal sugar levels in the blood. Thelander and Cholffin⁹ found low chloride and normal sugar values. In the case reported by Butler and associates,⁶ the sodium and chloride were low and the potassium was high. Before treatment the nonprotein nitrogen was elevated in every case in which the determination was made. With the exception of the blood sugar levels these findings are in keeping with adrenal cortical insufficiency.¹³ The observations made in our Cases 1 and 2 showing lowered values for total plasma base and bicarbonate and chloride levels support the theory that the underlying disturbance is related to adrenal dysfunction.

In classical Addison's disease the fasting blood sugar level is low and the patients are insulin sensitive.²⁰ An interesting discrepancy between the cases under discussion and those with Addison's disease is indicated by the normal blood sugar levels in three of our patients and in the two other patients for whom such data were given.^{9, 12} Talbot and associates,²¹ reporting again in 1947 on the patient of Butler and associates, also found a normal blood sugar and, in addition, normal insulin tolerance.

The lack of evidence of a disturbance in carbohydrate metabolism suggests that in this syndrome there may be a selective depression of salt and water-regulating substances, while the production of "S" hormone remains adequate.^{21, 22}

This suggestion is supported by two additional observations. Albright²² has defined the "S" hormone as the substance or substances elaborated by the adrenal cortex influencing the metabolism of carbohydrates. The excretion of 11-oxy corticosteroid-like substances (11-OCS) which, according to Talbot and

associates,²¹ reflects S hormone production, has been shown to be low in Addison's disease. By contrast a normal 11-OCS excretion was found by these workers in Butler's case of adrenal insufficiency with virilism.

The idea of a selective insufficiency with respect to salt and water metabolism in patients of this type is also in keeping with the histologic observations. In the microscopic picture of the adrenals of our patients, the zona glomerulosa was either absent or very poorly developed, while no significant morphologic aberrations were found in the fasciculata. The zona glomerulosa seemed largely replaced by big eosinophilic cells, many of which contained fuchsinophil granules in Cases 1, 2, and 3. There is evidence that, in the rat at least, it is the glomerulosa which produces salt- and water-regulating substances.²³⁻²⁶ The metabolic disturbances observed in our patients may thus be related to the lack of a zona glomerulosa.

Several authors have correlated the presence of fuchsinophil granules in the adrenal cortex with androgen production.^{1, 11, 16} Such granules were found in the outer layers of the cortex in three of our patients but could not be demonstrated in the fourth. Moreover, when present they were scanty in comparison with the description given by Broster and Vines¹ and Bratrud and Thompson.¹¹ However, in agreement with other studies we were unable to demonstrate these granules in our control material, and our inability to find them in Case 4 may have been due to our failure to use recently fixed material. We are inclined to regard the presence of fuchsinophil granules as significant.

The clinical and laboratory findings suggest a dissociation in the functions of adrenal cortex such that androgen or "N" hormone production is increased, salt and water regulating substances are decreased, and S hormone production appears unaffected. It is tempting to speculate that the S hormone producing cells remain intact while those influencing salt and water metabolism, presumably glomerulosal cells, are replaced by cells containing fuchsinophil granules, presumably producing excessive amounts of androgens. This hypothesis would correlate the entire clinical syndrome with the histologic picture. If this concept is valid it would appear logical to use desoxycorticosterone acetate (DOCA) rather than the complete cortical extract in the treatment of such patients as we have described.

SUMMARY

This paper deals with clinical, chemical, and pathologic observations on four infants who presented the picture of adrenal cortical insufficiency in association with bilateral adrenal hypoplasia as shown at autopsy.

The condition was found in 0.52 per cent of autopsies done on infants under 1 year of age, indicating a higher incidence than is suggested by the literature.

The familial pattern which was apparent in two of our patients remains unexplained and requires endocrinologic studies of the mothers of such infants.

In our own group and in all cases thus far reported the patients were either female pseudohermaphrodites with a characteristic deformity of the genitalia or else true males. In the latter, external manifestations of virilism are not apparent in early infancy.

The presenting clinical features were gastrointestinal symptoms, especially diarrhea, vomiting, and dehydration.

Serial chemical studies performed in two cases showed a lowering of the "total base," bicarbonate and chloride values in the plasma. The blood sugar levels were found normal in three patients.

Anatomic and histologic examination of the adrenals showed diffuse hyperplasia of the cortex with apparent replacement of the zona glomerulosa by eosinophilic cells which often contained fuchsinophil granules. A correlation of these findings with the clinical manifestations is suggested.

The physiologic disturbance appears to be one of overproduction with respect to N hormone and underproduction of substances regulating salt and water metabolism. The apparently intact carbohydrate metabolism differentiates these patients from those with true Addison's disease as regards the manifestations of adrenal insufficiency. Further studies of the carbohydrate metabolism in such patients are needed. It is suggested that the administration of DOCA and salt may be a complete substitution therapy in patients exhibiting this syndrome.

REFERENCES

1. Young, H. H.: *Genital Abnormalities, Hermaphroditism and Related Adrenal Diseases*, Baltimore, 1937, Williams & Wilkins Company.
2. Broster, L. R., and Vines, H. W. C.: *The Adrenal Cortex, A Surgical and Pathological Study*, London, 1933, H. K. Lewis and Co.
3. Grollman, A.: *The Adrenals*, Baltimore, 1936, Williams & Wilkins Company.
4. Haymaker, W., and Anderson, E.: *The Syndrome Arising From Hyperfunction of the Adrenal Cortex: The Adrenogenital and Cushing's Syndromes—A Review*, Internat. Clin. 4: 244, 1938.
5. Evans, F. R.: Specimen of Congenital Genito-urinary Abnormalities With Suprarenal Enlargement, Proc. Roy. Soc. Med. 30: 1190, 1937.
6. Butler, A. M., Ross, R. A., and Talbot, N. B.: Probable Adrenal Insufficiency in an Infant: Report of a Case, J. PEDIAT. 15: 831, 1939.
7. Dijkhuizen, R. K., and Behr, E.: Adrenal Hypertrophy in Infants: A New Clinical Entity of the Neonatal Period, Acta Pediat. 27: 279, 1940.
8. Wilkins, L., Fleischmann, W., and Howard, J. C.: Macrogenitosomia Precox Associated With Hyperplasia of the Androgenic Tissue of the Adrenal and Death From Corticoadrenal Insufficiency, Endocrinol. 26: 385, 1940.
9. Thelander, H. E., and Cholffin, M.: Neonatal Cortical Insufficiency (Addison's Disease) Associated With the Adrenogenital Syndrome, J. PEDIAT. 18: 779, 1941.
10. Thelander, H. E.: Congenital Adrenal Cortical Insufficiency Associated With Macrogenitosomia: Follow-up and Terminal Report, J. PEDIAT. 29: 213, 1946.
11. Bratrud, T. E., and Thompson, W. H.: Congenital Hyperplasia of the Adrenals, Staff Meet. Bull. Hosp. U. of Minn. 15: 25, 1943.
12. Darrow, D. C.: Congenital Adrenal Cortical Insufficiency With Virilism, Yale J. Biol. & Med. 16: 579, 1943-44.
13. Skelton, M. O.: Bilateral Adrenal Hypertrophy in Infancy, Arch. Dis. Child. 20: 135, 1945.
14. Hazelwood, G. A. D., and Strookman, T. A.: A Method for the Determination of "True" Sugar in 0.05 ml. of Blood, Biochem. J. 33: 920, 1939.
15. Fujiwara, T. F.: Ponceau-Fuchsin Stain for Androgenic Adrenal Cortical Cells: A Modified Technique, Arch. Path. 27: 1030, 1939.
16. Sudds, M. V. N.: The Cell Contents of the Cortex of the Suprarenal Gland, Endocrinol. 40: 895, 1940.
17. Hampton, H. P., and Keplor, E. J.: Addison's Disease: Treatment and Prognosis, Am. J. Med. Sc. 202: 264, 1941.
18. Patten, B. M.: *Human Embryology*, Philadelphia, 1947, The Blakiston Co.
19. Thorn, E. W.: *Textbook of Medicine*, Cecil, ed. 7, Philadelphia, 1948, W. B. Saunders Co., p. 1364.
20. Fraser, R., Albright, F., and Smith, P. H.: The Value of the Glucose Tolerance Test, the Insulin Tolerance Test and the Glucose-Insulin Tolerance Test in the Diagnosis of Endocrinologic Disorders of Glucose Metabolism, J. Clin. Endocrinol. 1: 297, 1941.

21. Talbot, N. B., Albright, F., Saltzman, A. H., Zygmantowicz, A., and Wixom, R.: The Excretion of 11 Oxoecorticosteroid-like Substances by Normal and Abnormal Subjects, *J. Clin. Endocrinol.* 7: 331, 1947.
22. Albright, Fuller: Cushing's Syndrome, *Harvey Lectures* 38: 123, 1942-43.
23. Swann, H. G.: The Pituitary Adrenocortical Relationship, *Physiol. Rev.* 20: 493, 1940.
24. Deane, H. W., and Greep, R. O.: A Morphological and Histochemical Study of the Rat's Adrenal Cortex After Hypophysectomy With Comments on the Liver, *Am. J. Anat.* 79: 117, 1946.
25. Greep, R. O., and Deane, H. W.: Cytochemical Evidence for the Cessation of Hormone Production in the Zona Glomerulosa of the Rat's Adrenal Cortex After Prolonged Treatment With Desoxycorticosterone Acetate, *Endocrinol.* 40: 417, 1947.
26. Deane, H. W., Shaw, J. H., and Greep, R. O.: The Effect of Altered Sodium or Potassium Intake on the Width and Cytochemistry of the Zona Glomerulosa of the Rat's Adrenal Cortex, *Endocrinol.* 43: 133, 1948.

SIMULTANEOUS CAPILLARY AND VENOUS HEMOGLOBIN DETERMINATIONS IN THE NEWBORN INFANT

LEON OETTINGER, JR., M.D.,* AND WILLARD B. MILLS, M.D.
NASHVILLE, TENN.

THE hemoglobin content of the blood of normal newborn infants is a subject of controversy. Values ranging from 15.5 Gm. per 100 ml. of blood¹ to 23.4 Gm. per 100 ml. of blood² have been reported as normal, and no explanation for the difference has been given.

It is the purpose of this paper to show that these values may be reconciled one with the other if the source of the blood on which the determination is done is considered. Capillary and venous bloods have been the usual sources for hemoglobin determinations reported in the literature, and we have used these two sources as the basis of our work. All previously reported work reviewed has been divided into these two groups in order to have standards of comparison.

Methods.—Blood samples used in this study were obtained within an hour of birth, at five days, and at three weeks of age. These dates were used because it was felt that within an hour the child would still reflect the conditions at birth. The five-day sample was obtained because this day was the usual time of discharge and would give some suggestion of the early changes occurring in hemoglobin concentration. The three-week period represented the neonatal checkup and gave us a period at which physiologic equilibrium should be established. Capillary blood was obtained from freely flowing puncture wounds of the great toe. Venous blood was obtained from the internal jugular vein. No anticoagulant was used, as dilutions were made immediately. Hemoglobin was determined as oxyhemoglobin on a standardized Klett photoelectrometer.

RESULTS

The hemoglobin content of the capillary blood in the one-hour specimens exceeded that of the venous blood in all individuals. The variations were between 0.6 Gm. per 100 ml. of blood and 8.2 Gm. per 100 ml. of blood with an average difference of 3.6 Gm. as is shown in Table I and Chart 1.

At five days it is seen that the capillary blood in general contains more hemoglobin than does the venous blood, and actually has a higher average content (20.5 Gm.) than it did on the first day, although the average difference between capillary and venous blood is less (2.2 Gm.). (Table I.) The range of differences is also less, being between 6.5 and -0.8 Gm.

In the blood drawn at three weeks this change is even more striking, the widest margin of difference being 2.9 Gm. with an average difference of 1.1 Gm.

From the Departments of Pediatrics of Vanderbilt University Medical School and Nashville General Hospital.

*Present address, 4614 Sunset Blvd., Los Angeles, Calif.

TABLE I. SIMULTANEOUS CAPILLARY AND VENOUS HEMOGLOBIN DETERMINATIONS IN THE NEWBORN INFANT

NO.	CAPILLARY			VENOUS			DIFFERENCES		
	1 HOUR	5 DAYS	3 WEEKS	1 HOUR	5 DAYS	3 WEEKS	1 HOUR	5 DAYS	3 WEEKS
1	21.2	19.5	14.9	13.0	17.4	13.8	8.2	2.1	1.1
2	21.2	24.1	15.0	13.0	22.1	13.4	8.2	2.0	1.6
3	25.7	—	—	18.7	—	—	7.0	—	—
4	24.3	21.6	16.5	18.5	16.7	17.1	5.8	4.9	-0.6
5	25.3	22.9	—	19.7	19.0	—	5.6	3.9	—
6	19.3	18.7	—	14.6	16.8	—	5.2	1.9	—
7	24.2	17.9	—	19.1	15.7	—	5.1	2.2	—
8	19.4	21.3	17.9	14.8	19.5	17.2	4.6	1.8	0.7
9	20.2	16.6	—	15.9	13.6	—	4.3	3.0	—
10	18.2	21.8	14.7	14.0	15.3	14.0	4.2	6.5	0.7
11	22.9	—	—	19.5	—	—	3.4	—	—
12	16.3	25.3	—	13.1	23.7	—	3.2	1.6	—
13	17.9	19.8	16.3	14.8	14.5	13.5	3.1	5.3	2.8
14	22.9	20.5	17.3	19.8	20.1	17.3	3.1	0.4	.0
15	20.2	23.7	17.1	17.6	19.5	18.2	2.6	4.2	-1.1
16	19.5	17.6	16.5	17.3	18.4	16.5	2.2	-0.8	.0
17	17.5	19.1	—	15.8	21.3	—	1.7	2.2	—
18	21.8	21.3	—	20.1	18.0	—	1.7	3.3	—
19	15.2	21.3	—	13.6	19.5	—	1.6	1.8	—
20	18.0	18.4	17.9	16.5	18.4	14.7	1.5	.0	3.2
21	20.2	16.6	14.8	18.8	16.6	11.9	1.4	.0	2.9
22	16.8	21.5	—	16.0	19.5	—	.8	2.0	—
23	18.5	21.8	—	17.9	18.8	—	.6	3.0	—
24	20.1	18.7	16.5	19.5	18.8	14.8	.6	-0.1	1.7
Average	20.3	20.5	16.3	16.7	18.3	15.2	3.6	2.2	1.1

SIMULTANEOUS CAPILLARY AND VENOUS HEMOGLOBIN

DETERMINATIONS ON 24 NEWBORN INFANTS

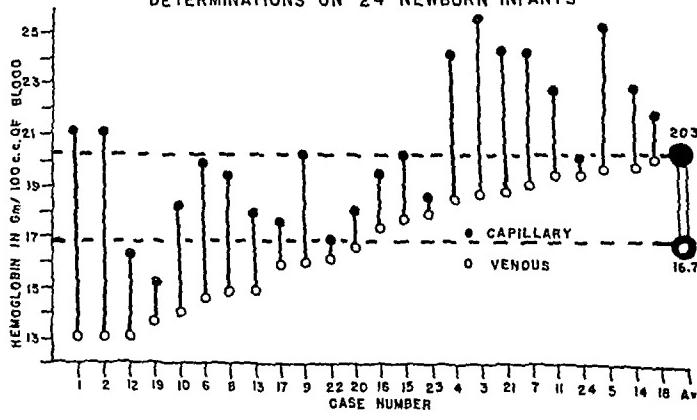


Chart 1.

This is compared with the maximum difference of 8.2 Gm. and an average of 3.6 Gm. difference on the first day and a maximum of 6.5 Gm. and an average of 2.2 Gm. on the fifth day.

DISCUSSION

In other hemoglobin studies, various authors have investigated either venous blood or capillary blood. If these results are grouped according to the source,

differences can be found similar to those reported here. The average of the values reported by the group using capillary bloods was 20.7 Gm. per 100 ml. of blood, while the average for the venous group was 16.9 Gm. per 100 ml. This is a difference of 3.8 Gm. and approximates the average difference of 3.6 Gm. found in this study on the first day.

TABLE II. HEMOGLOBIN VALUES FOR PERIPHERAL BLOOD

AUTHOR	JOURNAL	HEMOGLOBIN VALUE
Merritt, K. K., and Davidson, L. T.	Am. J. Dis. Child. 46: 990, 1933	23.4
Faxen, N.	Acta Pediat. 19: 1, 1937	23.4
Williamson, C. A.	Arch. Int. Med. 18: 505, 1916	23.3
Appleton, V. B.	J. Biol. Chem. 39: 369, 1918	22.3
Elvejhem, C. A., Peterson, W. H., and Medenhall, D. R.	Am. J. Dis. Child. 46: 105, 1933	22.2
DeMarsh, Q. B., Alt, H. L., and Windle, W. F.	J. A. M. A. 116: 2568, 1941.	21.3
Mackay, H. H. M.	Arch. Dis. Child. 8: 221, 1933	19.3
Andresen, B., and Ortmann, G.	Acta Med. Scandinav. 93: 410, 1937	19.0
Washburn, A. H.	Am. J. Dis. Child. 62: 530, 1941	19.0
Mitchell, J. M.	Am. J. Dis. Child. 38: 518, 1929	16.6
	Average:	20.7

TABLE III. HEMOGLOBIN VALUES FOR VENOUS BLOOD

AUTHOR	JOURNAL	HEMOGLOBIN VALUE
Kato, K.* and Emery, O. J.	Folia Hemat. 49: 106, 1933	18.0
Guest, G. M., Brown, E. W., and Wing, M.	Am. J. Dis. Child. 56: 529, 1933	17.9
Andresen, B., and Ortmann, G.†	Acta Med. Scandinav. 93: 410, 1937	16.3
Lucas, W. P., Dearing, B. F., Hoobler, H. R., Cox, A., Jones, M. R., and Smyth, F. S.	Am. J. Dis. Child. 22: 525, 1921	16.2
DeMarsh, Q. B., Alt, H. L., and Windle, W. E.	J. A. M. A. 166: 2568, 1941	15.5

*Kato and Emery do not give the source of their blood but a letter from the hospital where the work was done indicates the use of sinus blood of newborn infants.

†Andresen and Ortmann, in their article, reported the average value for both the sinus and peripheral hemoglobins. The values given in the above tables were recalculated by the present authors from the original data.

The cause of the variation between capillary and venous hemoglobin content in the newborn infant is not known. Wintrobe has described a similar variation in adults who had pernicious anemia and explains it as being due to macrocytosis with stasis in the capillaries (3). Macrocytosis is also found in the newborn infant, (4) and a similar explanation might be valid.

We believe another explanation which would fit well with the foregoing is that at the time of birth the capillaries are collapsed, with poor circulation, as evidenced by the blueness of the hands and feet in the newborn infant. The capillaries then act as a trap or sieve for the larger, heavier cells, preventing their return to the general circulation. Later, as the capillaries relax when the child recovers from the shock of birth, the peripheral and venous blood approach an equilibrium in hemoglobin content. The transitory rise occurring in the first few days after birth in capillary hemoglobin can be explained as a dehydration result.

SUMMARY

In summary, it has been found that the differences in the sources of the blood may partially explain some of the variations which have been reported in the hemoglobin values. It is also apparent that there is no constant relation between capillary and venous hemoglobins, although the capillary hemoglobin content is always the greater of the two and any comparison from day to day must always use hemoglobin from the same source.

REFERENCES

1. DeMarsh, Q. E., Alt, H. L., and Windle, W. E.: J. A. M. A. 116: 2568, 1941.
2. Merritt, K. K., and Davidson, L. T.: Am. J. Dis. Child. 46: 990, 1933.
3. Wintrobe, M. M., Schumacher, H. B., Jr.: J. Clin. Investigation 14: 837, 1935.
4. Guest, G. M., Brown, E. W., and Wing, M.: Am. J. Dis. Child. 16: 529, 1938.

SMALL BOWEL OBSTRUCTION IN INFANCY AND CHILDHOOD

A RADIOLOGICAL INTERPRETATION

CHARLES STORCH, M.D., BERNARD REDNER, M.D., AND RICHARD D. TURIN, M.D.
BROOKLYN, N. Y.

THE x-ray diagnosis of small intestinal obstruction in infants is extremely difficult. Ordinarily, the presence of air in the small bowel in older children and adults leads one to suspect small bowel pathology, but in infants such a condition is not abnormal. An x-ray diagnosis of early obstruction depends upon the differentiation between the small bowel containing normal amounts of gas and the small bowel containing abnormally large amounts of gas. The pediatrician is handicapped in making this distinction radiologically due to the paucity of material on this subject in the pediatric radiological literature. It is our intention to describe the gaseous state of the small bowel in its normal and in its obstructed phases as seen through x-ray.

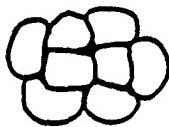
In adults and older children, the presence of an occasional gas-filled loop of small bowel on the x-ray picture is within normal limits. However, any marked degree of distention indicates the presence of a pathologic process. In infants it is normal to find gas in the small bowel up to the age of 2 or 3 years.¹ Gas appears in the stomach almost immediately after birth even when the infant is not fed during the first twelve hours of life. According to the studies of Wasch and Marek² the proximal portion of small intestine contains gas within the first hour of life. By the end of three hours the entire small bowel contains gas, and segments of the large intestine may also be visualized as a result of its gaseous content. By the end of eight hours there is a relatively large amount of gas in the small intestine as compared with the colon and, by twelve hours, the balance shifts so that the colon is the most prominent.

The normal small bowel, containing gas, is revealed on x-ray as a formless and shapeless mass with a hazy and washed-out appearance (see Figs. 1, A and 2). In contrast, in the obstructed small intestine, the formless segments assume a new shape dependent upon the gas trapped within the lumen of the bowel. The formless segment starts to bulge and then becomes "squared off" (see Figs. 1, B, 3, and 6). It would appear at first glance that if the bowel became distended with gas, the cross-sectional appearance would be that of a circle. However, the impingement of the distended loops, one upon the other, causes the small bowel to assume a square or rectangular appearance. For this reason we use the term "squared off." With increased amounts of gas we find that the x-ray appearance of the bowel is blacker, as found in any organ in which the aeration is increased. With the increased gas and the ballooning up of the bowel, a continuity of the small bowel segments will be established in the x-ray picture

From the Beth-El Hospital: Department of Pediatrics, Dr. Harry R. Litchfield, chairman; Department of Roentgenology, Dr. Max Dannenborg, Attending.



A. Formless - Shapeless
(Normal)



B. "Squaring Off"



C. Continuity



D. Hair Pin Loop



E. Layered Effect

Fig. 1.—Small bowel. A, Normal. B-E, Obstructed.



Fig. 2.—Normal small bowel, formless, shapeless, and hazy.

(see Figs. 1, C, 4, and 5). When the continuous loops turn upon themselves, the so-called "hairpin" turns may be noted (see Figs. 1, D and 5). With increasing distention, continuous loops will be noted to lie one above the other, a phenomenon which we prefer to call "layering" (see Figs. 1, E and 7) rather than the more conventional "stepladder effect." This layering may appear in cross section as a tier of "squared off" loops. Layering is a later manifestation of small bowel obstruction which even later may be associated with the formation of fluid levels in the bowel.

Finally, if doubt as to the presence or absence of small intestinal obstruction exists after inspection of the initial x-ray plate, another film should be taken a few hours later. This will provide the essential clue to the diagnosis by establishing the presence or absence of progressive distention of the loops of bowel (see Table I).

TABLE I*

NORMAL AIR		ABNORMAL AIR
Formless, shapeless		Squared off
Hazy, washed out		Increased blackening
		Continuity of bowel
		Hairpin turns
		Layering
		Fluid levels
		Progressive distention in follow-up films

*These characteristics are schematically represented in Fig. 1.

The presence of a gas pattern suggesting continuity in the colon may, of course, be normal, and this must be differentiated from the continuous pattern formed by obstructed small bowel. The small intestine may be identified by the presence of Kerkring folds which extend completely across the lumen of the bowel, while the plicae semilunares of the colon extend only partially across the lumen. Unfortunately, if gaseous distention is sufficiently increased, the Kerkring folds of infancy may disappear from the roentgenogram. A further point in the differential diagnosis of small and large intestine is the fact that the small bowel will be found to occupy a central position in the abdomen while the colon is found in the periphery (see Fig. 7). The outlines of the two sections of intestines are also different, the large intestine presenting hastrations and the small intestine having a smooth outline. These points will be brought out in a subsequent paper on large bowel obstruction.

Several brief case reports are appended to illustrate these remarks.

CASE 1—P., a 7-week-old male infant, was admitted on Nov. 26, 1947, with a history of obstipation for four days. There was vomiting of yellow fecal material for one day. No history of melena or grossly bloody stools could be obtained. Temperature was 99.6° F. on admission. The patient appeared moderately dehydrated with depression of the anterior fontanel. The abdomen was markedly distended with prominent superficial veins. There were no palpable masses in the abdomen. A bilateral hydrocele was noted, along with a right inguinal hernia. Rectal examination was negative, but a small amount of dark blood was passed immediately after withdrawal of the examining digit. Diagnosis postoperatively was volvulus of the small intestine with dilated bowel proximal

to the volvulus and collapsed bowel distally. X-ray findings prior to operation revealed evidence of obstruction in that there were squaring off of the loops of the bowel, fluid levels, and layering. The obstruction must have been in the small bowel, since all distended loops and fluid levels were located centrally in the abdomen. This is an example of late obstruction since fluid levels were present (see Fig. 3).

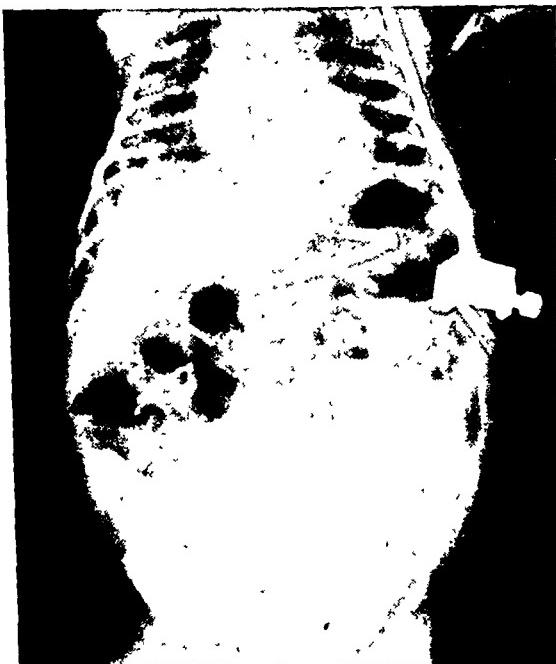


Fig. 3.—Obstructed small bowel illustrating principally "squaring off."

CASE 2.—R. O. H., a 2-week-old white male infant, was admitted March 21, 1948, with a history of vomiting for three days prior to admission. Stools had become progressively more scanty until admission, the last stool containing only mucus. The vomitus was yellow and had a fecal odor. Vomiting was projectile in type. The infant was markedly dehydrated on admission. A mass was noted in the right external inguinal canal leading to the scrotum. It was hard and irreducible. A reducible left inguinal hernia was noted on the left side. Evidence of incarcerated right inguinal hernia was found on operation. X-ray prior to operation revealed continuity of pattern, hairpin turns, squaring off, and increased blackness of the bowel. This is evidence of a relatively late stage of small bowel obstruction since many loops are involved (see Fig. 4).

CASE 3.—E., a 15-month-old white female infant, was admitted Sept. 19, 1947, with a history of anorexia for three days. Abdominal pain and vomiting began a few hours prior to admission. This was followed by a grossly bloody mucous stool. Temperature was 100° F. on admission. Rectal examination was negative, but there was blood on the examining digit on withdrawal. No masses were palpable in the abdomen. Operation revealed ileocecal intussusception with marked mesenteric lymphadenopathy. X-ray findings prior to operation revealed a continuous pattern of air in the bowel, hairpin turns, and layering in central position (see Fig. 5).



Fig. 4.—Obstructed small bowel illustrating principally continuity and layering.

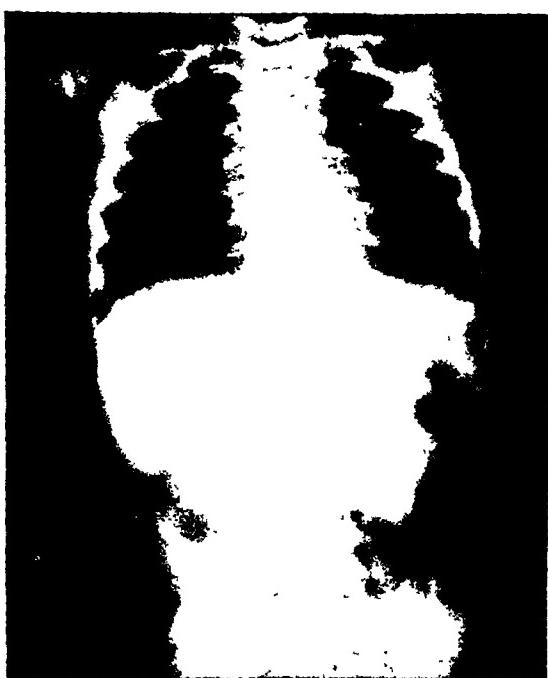


Fig. 5.—Obstructed small bowel illustrating principally continuity and hairpin loops.



Fig. 6.—Obstructed small bowel illustrating principally "squaring off" and continuity.



Fig. 7.—Obstructed small bowel illustrating principally layering, central position, and hairpin

CASE 4.—H., a 2-day-old white male infant, was transferred from the nursery on May 12, 1948. The infant regurgitated all feedings from the time of birth. Examination revealed a distended abdomen and palpable loops of bowel. There had been no bowel movements since birth. On the third day the patient had a very scant mucous stool. At operation a midgut volvulus was found. There was no large bowel distention. X-ray findings prior to operation were squaring off, continuity of pattern, and layering.

CASE 5.—C. L., a female Negro infant, was admitted on Nov. 29, 1948, about six hours after birth, with chief complaint of bleeding from the navel. The infant was pale, cyanotic, and had shallow respirations with the rate of five to six per minute. A marked systolic thrill was palpable over the precordium, accompanied by a harsh, blowing, systolic murmur. The hemoglobin was 100 per cent with 4.5 million red blood cells, 14,000 white blood cells with normal differential. The patient was given oxygen. An electrocardiogram revealed sinus tachycardia, prolonged A-V conduction time, and tendency to right axis deviation. Congenital heart disease was suspected (see Figs. 6 and 7). On the third hospital day the patient vomited bile-stained material continually. Small bowel obstruction was suspected and an x-ray of the abdomen was taken. This revealed squaring off (see Fig. 6), continuity of bowel, and layering (see Fig. 7). At autopsy there was marked dilatation of proximal two-thirds of the small intestine and compression of the lumen of the distal one-third. Consistent with the small bowel obstruction, there were also a pulmonary stenosis and patent interauricular septal defect.

SUMMARY

1. We have briefly endeavored to describe the characteristic gaseous states assumed by the small intestine when obstructed as revealed on x-ray. These abnormal phases are contrasted with the normal appearance of air in the small bowel in infants and children.

2. Five cases are briefly outlined, accompanied by their respective x-rays.

We are indebted to Mrs. Margaret Hamburger for her assistance in taking the various x-ray plates.

REFERENCES

1. Caffey, J.: Pediatric X-Ray Diagnosis, Chicago, 1945, Year Book Publishers, Inc., p. 347.
2. Wasch, M. G., and March, A.: The Radiographic Appearance of the Gastro-Intestinal Tract During the First Day of Life, *J. PEDIAT.* 32: 479, 1948.
3. Henderson, S. G.: The Colon in the Healthy Newborn Infant, *Radiol.* 39: 201, 1942.

A CORRECTION

Referring to my manuscript of "Botulism and Tick Paralysis" published in the June issue of THE JOURNAL OF PEDIATRICS, p. 716:

The identity of the tick which I reported as *Dermacentor variobolis* was challenged by the director of the Rocky Mountain Laboratory in Hamilton, Mont., as he states the dog tick is very rare west of the Cascades.

Dr. H. S. Sears, bacteriologist, and myself had thought we had properly established the identity of the tick, but sent the tick to the above laboratory where Mr. Kohls, their ixodologist, identified it as a female specimen of *Dermacentor andersoni*.

(signed) DON B. RICE

Case Reports

PHARYNGEAL INJURY CAUSED BY INGESTION OF GLASS CHIPPED FROM BABY-FOOD CONTAINER

JEROME S. LEOPOLD, M.D.
NEW YORK, N. Y.

THE occurrence of injuries in infants due to the ingestion of foreign bodies is not uncommon, but reports of injuries due to the swallowing of glass broken from food containers have received little notice in pediatric literature. Only two articles have been published at this writing. Steele¹ in 1948 reported two cases of mediastinitis due to the ingestion of glass from food containers. The patients were aged 18 months and 15 months, respectively. Both patients recovered after operation and following the use of penicillin and streptomycin. Steele states that, "In both instances it is probable that the breakage was due to the improper exertion of force at one particular point in prying the covers off the vacuum-packed glass containers." Directions for opening the glass containers suggest that force should be exerted at more than one point about the rim of the container. This is a very important procedure and should be practiced whenever the container is opened. Unfortunately, these directions appear only in very fine print on the container. In 1949 Hyde² reported a case (in a child aged 13 months) of peritonitis secondary to perforation of the bowel by glass chipped from a baby-food container. This patient was operated on and was then treated with penicillin, sulfathiazole, and streptomycin. Recovery followed this therapy. No other references could be found on this subject in an extensive search of the literature.

REPORT OF CASE

The following is a report of an infant whose pharynx was injured by the accidental swallowing of chipped glass from a food container.

On Feb. 26, 1948, D. K., a male infant aged 7 months who had been well previously, had suddenly cried as if in great pain and had vomited while being fed his dinner. The vomitus consisted of squash mixed with mucus and some bright red blood. There was some difficulty in breathing and swallowing. The squash had been obtained from a glass food container which, fortunately, was still in the refrigerator. Examination of the container revealed, to the mother's surprise, that a small part of the glass rim was missing. (Fig. 1.) Physical examination of the infant was essentially negative excepting for the throat, which was very congested. There was no evidence of bleeding, nor was there any visible injury of the pharynx. Immediate roentgenologic examination at the Lenox Hill Hospital failed to reveal evidence of a roentgen-opaque foreign body in the cervical region, chest, or abdomen. The temperature was 102° F. Therapy consisted of steam inhalations, sulfadiazine, and phenobarbital. At the end of twenty-four hours the difficulty in breathing and swallowing had disappeared, and physical examination was negative except for a slight congestion of the throat. Sixty hours after the initial vomiting, a piece of glass (Fig. 2) 8 mm. in length and 3 mm. in width was passed by rectum without any difficulty,

Formerly Director of Pediatrics, Lenox Hill Hospital; Clinical Professor of Pediatrics, New York University College of Medicine.

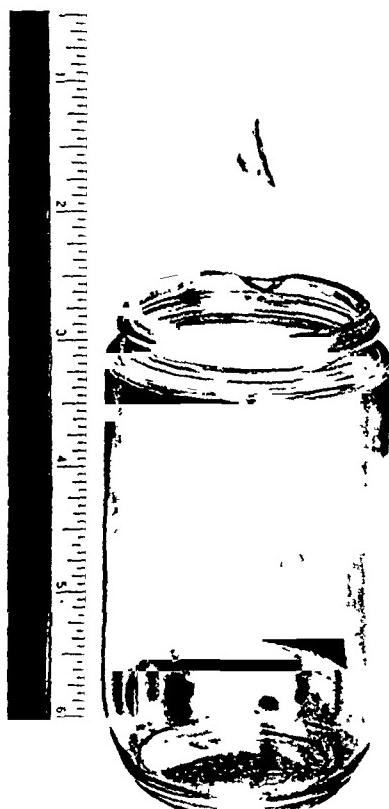


Fig. 1.—Baby-food container showing piece of glass chipped from container.

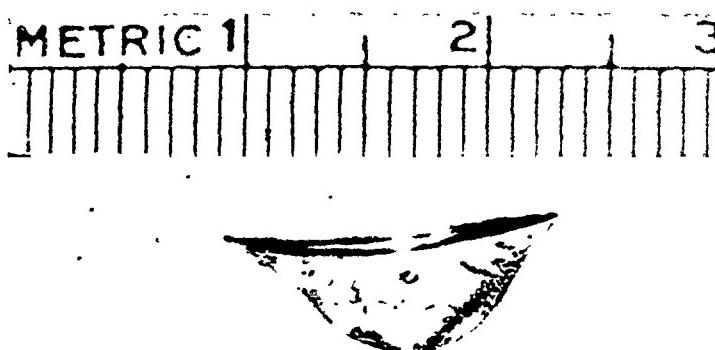


Fig. 2.—Glass chipped from baby-food container.

mixed with a soft stool. The infant has developed normally in every respect during the past year except for an occasional attack of diarrhea which has been controlled by appropriate diet.

SUMMARY

A case of injury to the pharynx in an infant, due to the ingestion of glass chipped from a baby-food container, is reported. A favorable outcome was apparently due to the relatively small size of the ingested glass. It is suggested that attention be given to the proper method of opening the food container, and to the careful inspection of the opened container to be certain that the glass container is intact.

REFERENCES

1. Steele, J. D.: Mediastinitis, *J. A. M. A.* 136: 554, 1948.
2. Hyde, J. S.: Peritonitis Due to Ingestion of Glass Chipped From Baby-Food Container, *J. PEDIAT.* 34: 219, 1949.

ACCIDENTAL THENYLENE HYDROCHLORIDE POISONING

REPORT OF A CASE WITH COMPLETE RECOVERY

HARRY S. SNYDERMAN, M.D.
PHILADELPHIA, PA.

THENYLENE Hydrochloride is the Abbott trade name for one of the newer synthetic antihistamine drugs now used for the treatment of allergic reactions. Thenylene Hydrochloride is supplied in 50 mg. tablets. The average adult dose is 50 mg. one to four times a day. The dose for children depends upon weight and age.

The common side effects of Thenylene Hydrochloride are drowsiness, dizziness, gastrointestinal irritation, and nervousness. Pharmacologic experiments in animals show that large overdoses of the drug cause convulsions which are followed by depression of the central nervous system.¹

CASE REPORT

W. D., a 20-month-old white male child, swallowed sixteen tablets of Thenylene Hydrochloride which had been prescribed for his mother's allergy. This was a total intake of about 800 mg. of the drug. The child swallowed the tablets at 11:30 A.M. At 12:20 P.M. the mother first noticed that the child was unusually drowsy. She gave the child milk and castor oil by mouth and immediately brought him to the admission room of the hospital.

On admission the child was convulsing, appeared markedly cyanotic, and was unconscious. His pupils were fixed and dilated. His neck was stiff. There was a marked tachycardia. The chest was clear and the abdomen was relatively soft.

Blood count and urinalysis showed no abnormalities.

Gastric lavage was started upon admission and continued until all the stomach contents had been removed. A hypodermoclysis of 2½ per cent glucose was started and the child was placed in an oxygen tent. At 1:20 P.M. one-half grain of phenobarbital sodium was given by hypodermic injection. A soapsuds enema was also given at this time. At 2:30 P.M. one-fourth grain of phenobarbital sodium was given by hypodermic injection. The convulsions continued. At 3:15 P.M. a mixture of sodium bromide grains 10 and chloral hydrate, grains 5, were given by rectum. Convulsions decreased in severity and the respirations became slower. Respirations continued to become slower and at 4:20 P.M. one-half ampule of caffeine sodium benzoate was given by hypodermic injection. By 10:00 P.M. the child was conscious and was calling for his mother. The child continued to improve and was discharged from the hospital forty-eight hours after admission.

DISCUSSION

The lethal dose of Thenylene Hydrochloride for mice is 190 mg. per kilograms when administered by oral route. It is 150 mg. per kilograms for cats.¹ To date there is no report of the lethal dose for man. Davis and Hunt report a case of Benadryl poisoning of a 2-year-old child in which death followed the

ingestion of 474 mg. of the drug.² The accidental poisoning by these antihistamine-like drugs should be guarded against. The fact that these preparations are sugar coated make them attractive to children.

SUMMARY

The accidental ingestion of 800 mg. of Thenylene Hydrochloride in a 20-month-old male child resulted in cyanosis, unconsciousness and convulsions, and was followed by a period of cardiorespiratory depression. The treatment consisted of the judicious use of a short-acting barbiturate plus normal supportive measures. The child improved in twelve hours and was completely recovered in twenty-four hours.

REFERENCES

1. Abbott Laboratories report on Thenylene Hydrochloride.
2. Davis, J. H., and Hunt, H. H.: Accidental Benadryl Poisoning, Report of a Fatal Case, J. PEDIAT. 34: 158, 1949.

ACTIVE INFANTILE TOXOPLASMOSIS

CAPTAIN THOMAS L. NELSON, MEDICAL CORPS, ARMY OF THE UNITED STATES, AND
MAJOR FRANK A. MANTZ, MEDICAL CORPS, UNITED STATES ARMY

TOXOPLASMOSIS, although still unusual, is being reported with increasing frequency. This case is thought to be of particular interest, for it demonstrates the appearance of the disease during its acute phase and its treatment with high dosage of the sulfonamides.

REPORT OF A CASE

A white female infant first became ill shortly after being hospitalized as a boarder at the age of 6 weeks. She was born at Gorgas Hospital, where she has been observed intermittently for a total period of seven months. During her seventh week and while in the hospital, she developed a mild left otitis media which subsided promptly with penicillin therapy.

In the eighth week of life she developed an unexplained fever. On physical examination the only abnormal findings were discovered in the eyes. It was impossible to define clearly any of the retinal vessels, the optic discs, or other structures behind the lenses. The diagnosis of the ophthalmologist at this time was severe retinal edema and edema of the optic discs. No evidence of increased intracranial pressure or abnormal neurological findings was elicited. The spinal fluid was crystal clear and under no increased pressure. Ten days later a right facial nerve paralysis appeared. Daily rectal temperatures ranged from 102 to 104° F. She was given short courses of sulfadiazine in low dosage, penicillin, and streptomycin with no apparent effect. Her eye findings and the facial paralysis continued, but no other abnormalities were discovered. She was transferred to a children's hospital in the continental United States on the twenty-sixth hospital day.

She remained febrile for the first thirty-two of the total forty-six days' observation at that institution. During this time her facial palsy disappeared, and she developed a ptosis of the left eyelid. There an ophthalmologist classified the eye changes as moderately acute choroiditis. While in that hospital she received treatment with streptomycin and combined sulfadiazine and sulfathiazole in undesignated dosage. After approximately three weeks of combined sulfonamide therapy her temperature became normal, and she was returned to the Canal Zone. An etiologic diagnosis was not made while she was in the United States.

After an afebrile period of four weeks, at the age of 4 months she suddenly developed a rectal temperature of 104° F. and again entered Gorgas Hospital, where she was studied for the ensuing six months. At this entry her retinas and optic discs again were edematous, and it was impossible to focus on any definite structure. The ptosis of the left eyelid was still present, and there was borderline microcephaly. No other abnormal physical finding or cause for her fever was discovered. On entry combined therapy with 0.13 Gm. each of sulfadiazine, Sulfamerazine, and sulfathiazole every four hours was instituted. This treatment continued over three and one-half months until the child was 7½ months old. Eight days after beginning this therapy, diminution in the retinal edema was noted, and it was possible to clearly visualize retinal vessels. In seven more days small white patches appeared scattered throughout both retinas.

From the Pediatric Section, Gorgas Hospital, and the Department of Pathology, Board of Health Laboratory, Ancon, Canal Zone.

By the twenty-fifth day white patches partially ringed with black pigment developed in the macular areas. More striking was the presence of black pigment dispersed within these lesions. In addition to these lesions, small white patches were seen outside the macular areas. During this period she continued to have an average rectal temperature of 101° F. with occasional spikes to 103° F.

At the age of 10 months her largest head circumference was 39.0 cm. (average for this age is 45.0 cm.¹); her head circumference had not increased in the previous four months, although an increase of 2.5 cm. would be expected normally.¹ The baby then had a length of 69.0 cm., and a weight of 15½ pounds. Her mental age and level of activity were estimated at from 3 to 4 months.

Throughout the illness there was a moderate normochromic, normocytic anemia but no leucocytosis or abnormality in the Schilling index. The corrected erythrocyte sedimentation rate was not elevated on several determinations. Repeated malaria smears were negative, and blood cultures during the course of the illness were sterile. Blood and spinal fluid serologic tests for syphilis and intradermal tuberculin tests up to 1:10 dilution were negative. The urine and stools were normal on repeated examinations, and the urine was free of lead.

Spinal fluid examinations from onset of the illness until the second admission to this hospital showed a progressive increase in leucocytes from 20 cells per cubic millimeter (11 polymorphonuclears and 9 lymphocytes) to 80 cells (all lymphocytes). The protein content was continuously elevated, reaching 113 mg. per 100 c.c. The chloride and sugar values were normal, and cultures were sterile. After fourteen days on combined sulfonamide therapy in this hospital, the patient's spinal fluid cell count was seven lymphocytes with 54 mg. per 100 c.c. of protein. At 10 months of age her spinal fluid cell count and chemistry determinations were normal.

No toxoplasma parasites were demonstrated on smears of spinal fluid before or during her last admission or on bone marrow smears. A total of eighty-four serially cut sections from a biopsy of the right quadriceps muscle examined under high-power magnification failed to show the presence of toxoplasma or other significant lesions. Part of this muscle was macerated and injected into two guinea pigs without the demonstration of toxoplasma infection. Complement fixation studies done on serum taken at 5 months of age prior to skin testing showed positive complement fixing antibodies for toxoplasma at a titer of 1:128.* Skin tests at 5 months and 7 months with chicken chorioallantoic membrane toxoplasma antigen at 1:100 and 1:1,000 dilutions showed no reaction.†² Repeated x-ray examinations of the skull at six-week to two-month intervals did not show significant lesions until the age of 9½ months, when scattered intracerebral calcifications most pronounced in the occipital area were first observed. X-ray examinations of mastoid areas, long bones, and chest showed no abnormalities. Spinal fluid taken on September 17 was inoculated into a guinea pig; this animal died spontaneously on October 24. Autopsy showed that the animal probably died of peritonitis due to *Pasteurella pseudotuberculosis*; multiple sections from the brain of this animal disclosed five typical large toxoplasma pseudocysts.

The mother of this child had a pregnancy complicated only by moderate hypertension. The mother, father, and 5-year-old sibling had no history of unexplained febrile illness, eruptions, or central nervous system disease. Examinations of their eye grounds were normal. The family had resided in the Canal Zone for seven years, coming here from California. The mother's serum was positive for complement fixing antibodies of toxoplasmosis at a titre of 1:32.* The sera of the father and sibling gave a negative complement fixation test.

*Test done through the courtesy of Joel Warren, Ph.D., Army Medical Department Research and Graduate School, Washington, D. C.

†Antigen obtained through the courtesy of Dr. Joel Warren.

Skin testing of the mother with the same antigen as used on the baby showed an area of erythema without induration measuring 0.8 by 0.6 cm. with 1:100 dilution and no reaction with 1:1,000.

DISCUSSION

The sulfonamides have been suggested for the therapy of toxoplasmosis on the basis of animal experimentation.³ We believe that this is the first human case in the acute phase of this disease that has received massive dosage of sulfonamides over a period of several months. This case is unique, since there have been active signs of the disease on which to evaluate therapy. We feel that the gradual change from an acute chorioretinitis to the healed form in the first twenty-five days of therapy with combined sulfonamides in this hospital may be significant. The spinal fluid became normal while on this therapy, and two and one-half months after discontinuing therapy was still normal. During the three weeks the patient was treated with sulfonamides in the United States her temperature became normal; following cessation of this therapy she was afebrile for four weeks and then relapsed. With massive dosage of sulfonamides in this hospital, her temperature did not become normal as did her eye and spinal fluid changes. This is due, perhaps, to interference with the temperature-controlling centers by the specific lesions of toxoplasmosis; this has been suggested previously by Paige and co-workers.⁴

The criteria for the diagnosis of infantile toxoplasmosis in this case have been chorioretinitis, microcephaly, intracerebral calcifications, and positive complement fixation tests for toxoplasma on both the patient and her mother. This patient also showed fever, mental deficiency, a normochromic, normocytic anemia, and increased protein and lymphocyte count in the spinal fluid. The finding of toxoplasma in the guinea pig inoculated with the patient's spinal fluid is of interest, but not conclusive, due to the natural incidence of toxoplasmosis in these animals.⁵ The skin test has been incompletely evaluated at the present time; the negative result in this baby is of questionable significance.⁶

SUMMARY

1. An unusual, nonfatal case of infantile toxoplasmosis which was observed in its acute phase during seven months of hospitalization is reported.

2. Treatment with high dosage of combined sulfonamide therapy may have modified the infection.

REFERENCES

1. Silver, H. K., and Deamer, W. C.: *J. PEDIAT.* 33: 167, 1948.
2. Warren, J., and Russ, S. B.: *Proc. Soc. Exper. Biol. & Med.* 67: 85, 1948.
3. Sabin, A. B., and Warren, J.: *Proc. Soc. Exper. Biol. & Med.* 51: 19, 1942.
4. Paige, B. H., Cowen, D., and Wolf, A.: *J. Dis. Child.* 63: 474, 1942.
5. Kean, B. H., and Grocott, R. G.: *Am. J. Path.* 21: 467, 1945.
6. Warren, Joel: Personal communication.

WILMS' TUMOR IN A NEWBORN INFANT

REPORT OF A CASE WITH AUTOPSY STUDIES

HANS HARTENSTEIN, M.D.

CHICAGO, ILL.

MALIGNANT tumors are rarely found in infancy and childhood. One of the most common malignant tumors occurring during these age periods is Wilms' tumor of the kidney.

This tumor has been the subject of considerable controversy regarding origin, histogenesis, and nomenclature. Some of the terms found to designate this neoplasm are: embryoma of the kidney, embryonal nephroma, mixed neoplasm of the kidney, nephroblastoma, adenosarcoma of the kidney, myosarcoma of the kidney. Willis¹ feels that the tumors included under these various names constitute one entity which he calls embryonic renal tumors and which, despite their varied appearance and components, arise from and consist of the immature renal blastema. Wells² prefers to unite these tumors under the heading of mixed malignant renal neoplasms or, using an eponym, Wilms' tumor of the kidney, the latter being probably the most widely used term at the present time.

Wells,² in 1940, reviewing malignant tumors in newborn infants, concedes to only five reported cases the validity of being true malignant congenital renal neoplasms. In addition to these five cases, malignant renal neoplasms occurring in premature or full-term stillborn or in older infants with symptoms or signs of the neoplasm since birth have been reported by Kocher,³ Landsberger,⁴ Little,⁵ Smirnowa-Zamkowa,⁶ Nicholson,⁷ and Dean and Pack,⁸ who reviewed the then existing literature; since 1940 Muto⁹ and Silver¹⁰ have each reported a case. However, it is questionable whether some of the above reports of renal tumors can be accepted as true Wilms' tumors, if Wells' criteria are applied.

Therefore, after examination of the American and foreign literature, which revealed only the above-mentioned cases of Wilms' tumor in newborn infants, the condition seems sufficiently rare to warrant reporting an additional case.

Clinical History.—The mother, Mrs. W. M., a 25-year-old, para ii, gravida iii, Negro female, was admitted to the Cook County Hospital of Chicago on May 6, 1948. She was in early labor. Family history and prenatal course were uneventful except for the occurrence of polyhydramnios during the present pregnancy. A roentgenogram of the abdomen taken because of this enlargement was interpreted as suspicious for twin pregnancy. Labor lasted for nine hours and forty minutes. Fetal heart tones were not heard on several occasions shortly prior to delivery, which was spontaneous and uncomplicated. The baby, a male, showed poor color and gasping respirations. He expired after two hours of life despite treatment with tracheal catheter, oxygen, and coramine. Before death the abdomen was noted to be distended and a firm, movable, round mass filling the entire left abdomen was palpated. Clinical diagnosis was left-sided congenital hydronephrosis.

Autopsy findings.—The body was that of a fairly well-developed Negro male measuring 45 cm. in length and weighing 2,150 Gm. The abdomen was 2.5 cm. above the xiphopubic line and its left half contained a firm, movable mass. On opening the abdominal cavity a large retroperitoneal mass in the left renal region was found which was firm in consistency. It was attached only

From the Department of Pathology, the Children's Division and the Hektoen Institute for Medical Research of the Cook County Hospital, Chicago.

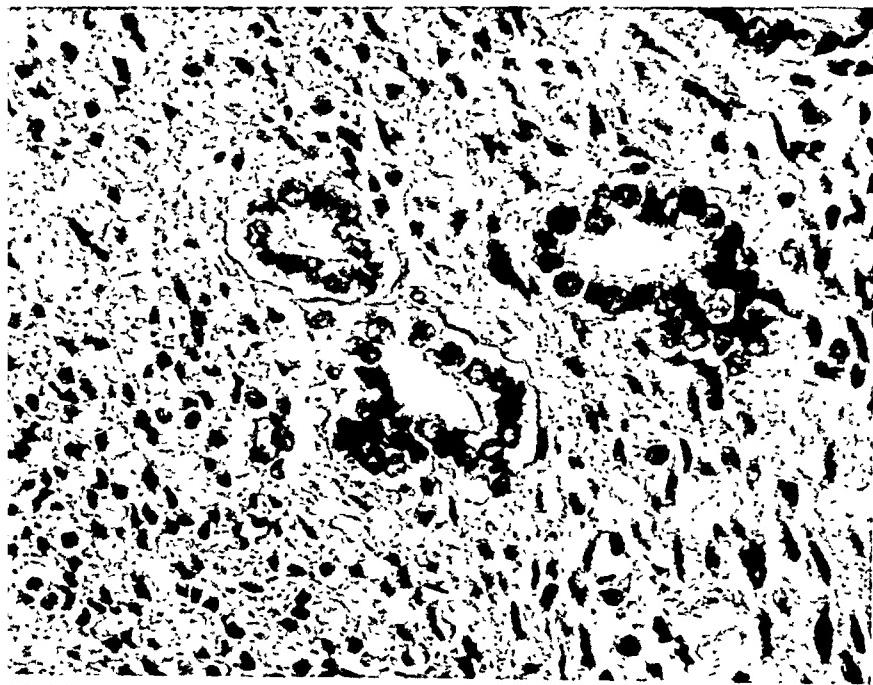


FIG. 1.—Tumor consisting of mesenchymal cells, arranged in interlacing bundles. In the lower left half of the picture a circumscribed area of embryonal cartilaginous tissue is seen. Glomeruli and tubules embedded in a loose, connective tissue stroma are noted ($\times 63$).



FIG. 2.—Cellular stroma consisting of spindle-shaped and polygonal cells. Three well-differentiated tubules are seen ($\times 286$).
FIG. 2.—Cellular stroma consisting of spindle-shaped and polygonal cells. Three well-differentiated tubules are seen ($\times 286$).

to the left renal artery and vein and to the left ureter, which was patent and led to the bladder. The mass was in place of the left kidney, measured 7 by 5 by 3.5 cm., was well-encapsulated, and shelled out easily. The left adrenal gland was separated from the superior aspect of the tumor by loose areolar connective tissue. On section the tumor was seen to be composed of light tan whorls of connective tissue and lobulated areas of pink-reddish tissue with a firm consistency. The capsule was a thin layer of dense connective tissue and was not penetrated by the tumor mass. No renal pelvis was present.

Sections of the tumor mass were fixed in formalin and stained with hematoxylin and eosin, Masson trichrome method (Goldner's modification), Mallory connective tissue stain, and impregnated with silver, using Gomori's method.

Histologic examination revealed considerable variation of appearance throughout different parts of the specimen. Practically the entire renal parenchyma was replaced by tumor tissue.

The periphery of the tumor was surrounded by a loose connective tissue capsule in which thin-walled blood vessels were seen. Some extravasation of red blood cells was also noted in this area. Thin septa of loose connective tissue with well-developed glomeruli and tubules were seen between undifferentiated vascular mesenchymal tumor tissue which formed the greatest part of the tumor. In some areas the tumor tissue appeared edematous and even myxomatous, while in other areas it was dense and very cellular. Broad bands of spindle-shaped and polyhedral cells were arranged in interlacing bundles, occasionally intermingled with smooth muscle fibers and islands of well-circumscribed embryonal cartilaginous tissue. Scattered throughout the stroma isolated tubules were seen which were lined by flattened, almost endothelial-like epithelial cells.

Closer examination of the stroma revealed pleomorphism of the tumor cells. The nuclear membrane of the spindle-shaped and polygonal nuclei was sharply delineated and the chromatin was finely and uniformly dispersed. No mitotic figures were noted.

Silver-impregnated sections revealed a rich reticulum network with argentophilic fibers surrounding the mesenchymal tumor cells.

Gross examination of the lungs revealed them to be almost completely collapsed. Microscopic examination confirmed the gross diagnosis of atelectasis.

The other organs showed no pathologic findings.

DISCUSSION

As this tumor was found at autopsy in an infant 2 hours of age, it appears unquestionable that it must have developed during intrauterine life. This case, therefore, serves as a good example of the occurrence of malignant tumors in the unborn fetus which may be of importance for theories of the pathogenesis of malignant neoplasms.

An interesting feature from the microscopic point of view is the finding of islands of normal renal tissue with well-developed glomeruli and tubules. These glomeruli were not the so-called preglomeruloid structures nor abortive glomeruli of the mesonephron described frequently as occurring in such tumors. Therefore, the question arises whether these structures are the remnants of normal renal parenchyma or a part of the tumor which has reached complete differentiation in these areas.

This finding of normal renal tissue within a Wilms' tumor has not, to the author's knowledge, been stressed in previous reports of such tumors occurring in the newborn infant.

SUMMARY AND CONCLUSION

A case of a Wilms' tumor in a 2-hour-old infant is reported, pointing to the intrauterine development of the tumor.

Areas of normal renal parenchyma were found within the tumor tissue. The question is raised whether these areas represent tumor tissue which has reached complete differentiation or remnants of normal renal tissue.

REFERENCES

1. Willis, R. A.: *Pathology of Tumors*, St. Louis, 1948, The C. V. Mosby Company, p. 925.
2. Wells, H. G.: Occurrence and Significance of Congenital Malignant Neoplasms, *Arch. Path.* 30: 535, 1940.
3. Kocher, T.: Eine Nephrotomie wegen Nierensarkom, *Deutsche Ztschr. f. Chir.* 9: 312, 1877-78.
4. Landsberger, H.: Zur Kasuistik der kongenitalen Nierengeschwuelste, *Berliner klin. Wehnschr.* 14: 497, 1877.
5. Little, J. L.: Sarcoma of the Kidney, *N. Y. Med. J.* p. 341, March 29, 1884.
6. Smirnowa-Zamkowa, A. J.: Die Frage ueber "gemischte embryonale Geschwuelste," *Ztschr. f. Krebsforsch.* 22: 218, 1925.
7. Nicholson, G. W.: An Embryonic Tumor of the Kidney in a Foetus. *J. of Path. & Baet.* 34: 711, 1931.
8. Dean, A. L., Jr., and Pack, T.: Embryonal Adenosarcoma of the Kidney, *J. A. M. A.* 98: 10, 1932.
9. Muto, K.: Ein Fall von Nierensarkom bei einem Siebenmonatlichen Foetus, *Gann.* 31: 102, 1940.
10. Silver, H.: Wilms' Tumor, *J. PEDIAT.* 31: 643, 1947.

Clinical Conference

CONFERENCE AT DUKE HOSPITAL OF DUKE UNIVERSITY
SCHOOL OF MEDICINE, DURHAM, N. C.

GRANT TAYLOR, M.D., CONFERENCE CHAIRMAN

Mycotic Infections in Children (The Budding Yeasts as Agents of Disease)

FUNGUS infections in children occur frequently. For convenience, they may be divided into: (1) those infections which attack the skin, hair, and nails; (2) those which involve the skin and subcutaneous tissues; and (3) the systemic mycotic infections. Some of the etiologic agents in the latter group appear as budding, yeastlike forms and give rise to grave disorders which frequently are diagnosed incorrectly, poorly treated, and generally thought to be rare.

Dr. J. S. HARRIS (Associate Professor of Pediatrics).—The apparent rarity of fungus diseases is due to two major factors: (1) failure to think of and recognize these diseases and (2) their geographic distribution. Although moniliasis and cryptococcosis are widespread, the other diseases are delimited by definite geographic boundaries. For example, North American blastomycosis occurs exclusively on the North American continent. In the United States, however, the preponderance of reported cases occurs in the Mississippi Valley and the southeastern area. South American blastomycosis, on the other hand, is found only in South America, particularly in Brazil. Histoplasmosis, although reported throughout the world, has its greatest incidence in the Mississippi Valley. Great differences of reported incidence may occur in adjacent areas; for example, histoplasmosis is common in Tennessee and very rare in adjacent North Carolina. In spite of the endemicity of these infectious agents, the normal migrations of people, now amplified by speed and ease of transportation, are such that all physicians and clinics should be alerted to these diseases. The possibility of their occurrence should be considered in the differential diagnosis of all obscure infectious diseases.

Dr. N. F. CONANT (Professor of Medical Mycology).—There are five fungus infections in which the etiologic agent appears as a budding, yeastlike organism in the lesion or in materials from the lesion; namely, cryptococcosis, moniliasis, histoplasmosis, North American blastomycosis, and South American blastomycosis.

The fungus which causes cryptococcosis, *Cryptococcus neoformans*, appears in clinical materials as a capsulated, round, thick-walled, budding, yeast-

like cell, 5 to 15 μ in diameter. Such capsulated organisms can be demonstrated clearly in India ink preparations in which the ink particles outline the capsular material. *C. neoformans* remains yeastlike in culture both at room temperature and at 37° C. (98.6° F.). On Sabouraud's glucose agar the colonies are mucoid and tan to brown in color. Capsules may be demonstrated also by India ink preparations of materials from these cultures. The capsule is diagnostic for *C. neoformans*, but animal pathogenicity, especially for mice, also should be established.

The fungus which causes moniliasis, *Candida* (*Monilia*) *albicans*, appears in clinical materials as oval, thin-walled, budding, yeastlike cells 2.5 to 6 μ in diameter. An occasional pseudomycelium also may be seen. *C. albicans* remains yeastlike in culture both at room temperature and at 37° C. (98.6° F.). On Sabouraud's glucose agar the colonies are smooth, creamy, and honeycombed in the center, and have a distinct yeasty odor. The thin-walled, oval, budding cells may be demonstrated on the surface of the agar and the pseudomycelium in the subsurface growth extending into the agar beneath the colony. The lack of a capsular substance and the presence of pseudomycelia distinguish this fungus from *C. neoformans*. It also may be distinguished from other species of *Candida* by its specific sugar fermentations and by its pathogenicity for rabbits.

In histoplasmosis caused by *Histoplasma capsulatum* the fungus appears in macrophages as an intracellular, oval body 2 to 4 μ in diameter. *H. capsulatum* parasitizes the reticuloendothelial system and may be demonstrated in Giemsa-stained smears of peripheral blood, bone marrow, sputum, exudate from mucosal lesions, and impression smears of tissues (nodes). On sealed blood agar slants at 37° C. (98.6° F.), yeastlike colonies which resemble *Staphylococcus albus* are developed. Microscopically, the fungus appears as small, oval, budding cells, 2 to 4 μ in diameter, which resemble the tissue phase. On Sabouraud's glucose agar at room temperature, however, *H. capsulatum* grows as a typical mold and, microscopically, is composed of septate, branching hyphae from which characteristic thick-walled tuberculate chlamydospores are produced. These structures are diagnostic and may be used for accurate identification of the fungus. When this moldlike growth is transferred to sealed blood agar slants at 37° C. (98.6° F.), the culture reverts to the yeast phase. The filamentous growth of *H. capsulatum* at room temperature distinguishes this fungus from the two above and the characteristic tuberculate chlamydospores distinguish it from all other filamentous fungi. Pathogenicity tests in mice may be attempted for either the yeast or filamentous culture.

The fungus which causes North American blastomycosis, *Blastomyces dermatitidis*, appears in clinical materials as large, thick-walled, single budding yeastlike cells, 5 to 15 μ in diameter. On blood agar at 37° C. (98.6° F.), the colonies are yeastlike, smooth, or wrinkled, and show microscopically the budding, yeastlike cells of the tissue phase. On Sabouraud's glucose agar at room temperature, *B. dermatitidis* grows as an atypical mold and microscopically is composed of septate, branching hyphae from which round to pyriform conidia 5 to 8 μ in diameter are produced. When this type of growth is transferred

to blood agar slants at 37° C. (98.6° F.), the culture reverts to the yeastlike tissue phase. The small, smooth spores of the filamentous cultures distinguish *B. dermatitidis* from *H. capsulatum* and the large, round, thick-walled budding cells in cultures at 37° C. (98.6° F.) distinguish *B. dermatitidis* from the yeast phase of *H. capsulatum*. Pathogenicity tests in mice may be attempted for either the yeast or filamentous culture.

The fungus which causes South American blastomycosis, *Blastomyces brasiliensis*, appears in clinical materials as large, thick-walled, multiple budding, yeastlike cells 10 to 60 μ in diameter. On blood agar at 37° C. (98.6° F.) the colonies are yeastlike, smooth or rough, and show, microscopically, the multiple budding, yeastlike cells of the tissue phase. On Sabouraud's glucose agar at room temperature the colonies are moldlike, slow growing, heaped, and wrinkled. These colonies are composed of septate, branching hyphae with numerous chlamydospores. When this moldlike growth is transferred to blood agar at 37° C. (98.6° F.), the colonies revert to the yeastlike phase. *B. brasiliensis* is distinguished from *B. dermatitidis* by its slow growth and lack of spores on Sabouraud's glucose agar at room temperature and multiple budding cells in tissue and culture at 37° C. (98.6° F.). Pathogenicity tests in mice may be attempted for either the filamentous or yeast phase.

Since *H. capsulatum*, *B. dermatitidis*, and *B. brasiliensis* appear yeastlike in tissue and in culture at 37° C. (98.6° F.) but are filamentous on Sabouraud's glucose agar at room temperature, it is necessary to be familiar with both morphological forms so that a diagnosis may be made immediately. This dimorphism, a characteristic of many fungi which cause systemic infections, need not be confusing after one becomes familiar with the different tissue and cultural forms.

DR. HARRY B. O'REAR (Resident in Pediatrics).—The first case is that of a 5-year-old Negro boy who was admitted Nov. 10, 1948, with a complaint of a swollen, tender area over his left eye of four days' duration. One year prior to admission the child developed a draining sinus on the left side of his nose. A second draining sinus developed six months later. Four days prior to admission a swollen, tender area on the child's forehead over the left eye was noted and he was referred to this hospital for treatment. Positive physical findings were: A soft, tender, swollen area (4 by 5 cm.) over the left frontal region. There were draining sinuses on the medial side and below the left eye. X-rays revealed extensive erosion of the left frontal bone, the roof of the left orbit, and the medial aspect of the right orbit. The child had a triangular section of the left frontal bone excised, the pathologic examination of which revealed the *Blastomyces* organism. Smears and cultures of material from the draining sinuses were positive for *B. dermatitidis*. The skin test for *Blastomyces* was positive, but the complement fixation was negative. Therapy consisted of desensitization with *Blastomyces* vaccine and, after three weeks of desensitization, potassium iodide by mouth. Serial x-rays revealed extension of the osteolytic process for seven weeks after admission. The child was discharged three months after admission, therapy to be con-

tinued as an outpatient. At the time of discharge the sinus tracts were healed and the child was afebrile. Complement fixation at this time was 1:8. Diagnosis was blastomycosis.

The second case is a 13-year-old Negro boy admitted Dec. 15, 1948, with a history of a cough and pain in the left chest of three weeks' duration. Twelve hours before admission he complained of pain in the abdomen with nausea and vomiting. On admission, the patient had a temperature of 39.5° C. (103.1° F.) and a white blood cell count of 28,000. The physical findings were consistent with those of a localized area of consolidation. There was generalized mild abdominal tenderness without rigidity. No abdominal masses were felt. X-ray of the chest revealed a localized area of consolidation radiating down from the left hilum with an area in the center suggestive of cavitation. O. T. 1:100 was one plus at the end of forty-eight hours. Sputum culture revealed a variety of gram-positive and -negative organisms. Acid-fast stain of sputum was negative. On admission the patient was placed upon penicillin and sulfadiazine therapy without clinical response. The addition of streptomycin to the therapy produced no response. Physical findings remained the same and fever remained elevated although the patient was ambulatory. The cervical lymph nodes enlarged and two subcutaneous abscesses developed, one in the right mamma and the other over the right deltoid. Six weeks after admission sputum cultures were reported positive for *B. dermatitidis*. Complement fixation for Blastomyces was positive in serial dilution to 1:16. Blastomyein skin test was positive 3+. The patient was started on Blastomyces vaccine, desensitization, and, after three weeks, potassium iodide therapy was begun. Culture of material from one of the subcutaneous abscesses gave a pure growth of Blastomyces. Throughout his hospital stay the patient continued to have a fever and the physical findings remained unchanged. X-ray of the chest showed no improvement in the pneumonic process. The patient was discharged at the end of three and one-half months to continue on the Blastomyces vaccine desensitization and potassium iodide therapy. Diagnosis was blastomycosis.

The third case was a 2½-month-old white boy admitted because of recurrent lesions on the tongue and scrotum. The mother's past history was significant in that she had a Monilia infection during the pregnancy. The infant, at the age of 6 weeks, again at the age of 2 months, and again just prior to admission, had developed lesions on the end of his tongue and at the base of his penis which appeared first as small papules and became larger and subsequently hemorrhagic. The temperature became elevated with each flare-up of the lesions. The lesions seemed to respond to treatment with sulfonamide and penicillin.

Positive physical findings were as follows: There was a circumscribed, swollen, hemorrhagic lesion on the right lateral and ventral aspects of the tongue which bled freely on pressure. There was a pigmented area at the base of the penis which marked the site of the scrotal lesion. On admission

the infant was placed upon penicillin therapy and the tongue lesion was sprayed with a penicillin solution. There was some improvement, but the scrotal lesions became active. Cultures of the lesions revealed a variety of organisms, but skin tests to the bacterial vaccines were negative. A Monilia skin test was found to be positive and fungus cultures of the lesions were found to be positive for *C. albicans*. The infant was placed on gentian violet therapy parenterally and locally with prompt improvement of the lesions. Desensitization with Monilia vaccine was begun. Healing of the lesions continued and there were no further recurrences. The infant's hospital course was complicated by frequent daily convulsions for a short period. He was discharged at the end of two months to continue with the desensitization therapy. Diagnosis was moniliasis of skin and mucous membranes.

DR. D. T. SMITH (Professor of Bacteriology).—To obtain the best results in the treatment of mycotic infections* it is essential to study the immunologic status of the patient. The presence or absence of hypersensitivity can be determined by intracutaneous skin tests with either vaccines or with special antigens such as histoplasmin, coccidioidin, or blastomycin. The determination of hypersensitivity is essential since a marked exacerbation of the lesions can occur in hypersensitive individuals after the administration of therapeutic agents, in particular, iodides. This response can be minimized by desensitization prior to iodide therapy. Immune bodies in the serum of the patient can be measured in terms of agglutinins in moniliasis or in terms of complement fixing antibodies in blastomycosis, coccidioidomycosis or histoplasmosis. The determination of the immune bodies is important for prognosis. A relatively high titer usually signifies an extensive infection, usually generalized and systemic in nature. Absence of or low titers of immune bodies may mean a mild infection, or, on the other hand, the terminal stage of a severe infection (anergic phase). A similar decrease in hypersensitivity to skin tests may also occur in severe and terminal infections, and thus be indicative of a poor prognosis.

The two cases of blastomycosis had positive skin tests to Blastomyces vaccine. The treatment, therefore, consisted of desensitization with the Blastomyces vaccine followed by the administration of potassium iodide. The prognosis is good in Case 1 in spite of the extensive destruction of the frontal bone, since the complement fixation was at first negative and only became positive after therapy. The prognosis in Case 2 is not so good because of the presence of a high titer of complement fixing antibodies before treatment. This prognosis was confirmed by the development of metastatic lesions while the patient was under treatment.

The case of moniliasis showed marked hypersensitivity to the Monilia vaccine and therefore desensitization was necessary before the administration of iodide. The patient did not have agglutinins in his serum for Monilia. Gentian violet is useful in treating moniliasis, but is not a substitute for an immunologic study and for desensitization where this is indicated.

*Smith, D. T.: Mycotic Infections in North Carolina, N. C. Med. J. 10: 167, 1949.

Psychologic Aspects of Pediatrics

MOTION SICKNESS IN CHILDREN

HARRY BAKWIN, M.D.
NEW YORK, N. Y.

MOTION sickness is the term used to designate the group of symptoms which result from repeated oscillatory movements of the body. It includes seasickness, ear sickness, airsickness, trainsickness and elevator sickness. All of these are closely related in etiology and symptomatology and respond to the same therapeutic agents.

The incidence is high. It has been estimated that under severe conditions only 20 per cent of unacclimatized persons will remain entirely free of seasickness. Maitland¹ states that all normally constituted people are susceptible to some definite type of movement.

Car sickness is more common in children than in adults. It usually makes its appearance during the second or third year of life but, contrary to general opinion, it does occur occasionally in infants. Its infrequency at this age may be due to the fact that infants are generally kept lying down, in which position symptoms are less likely to occur.

The characteristic manifestations of car sickness are nausea and vomiting. There may be only headache, anorexia, and malaise. Nausea is a normal response to violent oscillating movements. In the individual with the motion sick diathesis, the threshold is lowered and nausea appears in response to minimal movement. The tendency to this condition is increased by excitement, fear, apprehension, agitation, irritation, physical illness, a stuffy atmosphere, offensive odors, the sight of vomiting. Vomiting may or may not accompany the nausea. Some children with this ailment have great difficulty in vomiting and retch violently while others vomit readily.

The frequency of attacks varies widely, some children developing symptoms whenever exposed while others suffer only occasionally. There is no definite relation to meals. The condition is usually hereditary, occurring in several members of the same family.

Seasickness and airsickness are less common in children than in adults. Infants are affected occasionally. The symptoms are generally more severe than those of ear sickness. At first there is quietness, frequent yawning, apathy, depression, and a desire to be left alone. In addition there may be headache, anorexia, and excessive salivation. Vomiting then takes place, with or without preceding nausea. The vomiting may occur frequently or only once a day. It may or may not give temporary relief of symptoms. In some instances there is retching without vomiting and this is apparently more exhausting than true

vomiting. Pallor and cold sweat are early signs. A small proportion of the population (about 5 per cent) is severely affected when exposed to the sea and seems never to become acclimatized.²

Hill³ attributes the symptoms of seasickness to a disturbance of the autonomic nervous system. He recognizes two forms,¹ a vagotonic form, most common in men, in which the principal symptom is headache with malaise and bradycardia. Nausea is generally absent. Vomiting is unusual but, if present, it occurs at long intervals and gives temporary relief.² In the sympathetonic form, which is more common in women, nausea and vomiting are frequent and headache rare. The heart rate is rapid.

It is probable that several mechanisms operate in the production of motion sickness.⁴ Some observers believe that the syndrome is primarily psychogenic. The psychic influences which exaggerate the tendency to motion sickness have been enumerated above. Neurotic and apprehensive individuals are especially susceptible. That certain persons develop symptoms shortly after boarding a ship prior to sailing is well known. Even dogs in whom motion sickness has been experimentally induced may vomit later on upon entering the room containing the apparatus. Seamen severely incapacitated by seasickness may be able to overcome some of their discomfort when distracted by the activities necessitated by naval engagements. Against the viewpoint that the psychologic factor is a primary one is the hereditary nature of the ailment and its occurrence among animals, notably dogs, cats, horses, monkeys, birds, poultry, and others. Even fish transported from the Galapagos Islands to the New York Aquarium were reported to have been seasick!⁵ It is generally agreed that psychologic factors alone account for a certain number of cases and that, in general, the clinical picture is readily influenced in this way.

A widely held view is that the difficulty lies in the vestibular apparatus. McEachern, Morton, and Lehman⁶ emphasize that, though more of the available evidence favors this hypothesis than any other, other possible mechanisms should not be disregarded. They state: "Much of the evidence which tends to incriminate the vestibular apparatus has been obtained by direct stimulation of the labyrinths and not by reproduction of the bodily movements which ordinarily cause motion sickness. Vestibular irritation may not be motion sickness despite the similarity of symptoms."

Poppen⁶ suggested that the circulatory changes produced in the large vessels of the neck by the up and down movement of a ship may stimulate the carotid sinus with consequent changes throughout the autonomic nervous system. Relief of symptoms has been reported in a number of seasick individuals by the application of a collar specially designed to support the structures of the neck. Pflanz⁷ emphasized the importance of rhythmic changes in the blood flow to the brain.

Many authors attribute the symptoms of motion sickness to the effects of gross movements on the abdominal viscera. Keevil⁸ states that the vertical movement of a ship produces a drag on the mesentery, thereby constricting the third portion of the duodenum with resulting dilatation of the proximal duodenum and vomiting. Against this view is the absence in motion sickness of

epigastric pain, a symptom usually associated with constriction of the duodenum. Others have suggested that the tug on the mesentery itself may be sufficient to produce symptoms and that the alternate engorgement and anemia of the liver is a factor. Maitland¹ claims to have alleviated the symptoms by the use of a snug abdominal belt.

Vision may be a factor, too. The liability to seasickness is diminished when the eyes are closed. Persons are more likely to develop seasickness while watching foam-crested waves or currents in the ship's wake.⁹ In some individuals the liability to seasickness is diminished when the eyes are closed. The susceptibility of dogs to motion has been reduced by suturing the eyelids. However, the visual element seems to be only a contributing factor since blind persons are subject to seasickness and the attacks may occur in the dark. Apparently various types of stimuli may set off the syndrome and different conditions modify the picture in different individuals.

Treatment.—Motion sickness usually persists throughout life but it tends to improve as the child grows older. If treated calmly, without excessive solicitude or comment, it is usually mild. Training is useful and the disappearance of car sickness as the child grows older is probably attributable in part to this factor, just as the seaman develops a relative immunity to seasickness. For training purposes, the child should be taken on rides of gradually lengthening duration. This not only permits gradual adjustment to movement but the child's success, when he is taken on short rides, serves to relieve apprehension and to bolster self-confidence. Conn¹⁰ has found the play-interview a useful method of treatment. Allowing the child to play with dolls in toy streetcars and automobiles helps him to express his feelings and thoughts in an impersonal way and makes him aware of the fact that he has contributed to his own discomfort. The drinking of liquids should be avoided before taking a trip. Salty foods may have a soothing effect.

Of the many drugs which have been tested for the relief of motion sickness, those found to have the greatest value are either alkaloids of the belladonna group or general sedatives. Scopolamine (hyoscine) has proved to be one of the most effective drugs in preventing seasickness and airsickness. A disagreeable side effect is dryness of the mouth, but this can be avoided by using the aminoxide hydrobromide of scopolamine. The dose for a 5-year-old child is 0.3 mg. The efficacy of scopolamine is presumed to rest upon its sedative and tranquilizing central effect and its action as an antagonist of acetylcholine. The power of inhibiting excessive motility of the gastrointestinal tract appears to be of major importance. Bromides and phenobarbital are also valuable aids in treatment.

Recently Dramamine (Searle), an antihistaminic drug, has been recommended as a safe and effective agent for the prophylaxis and treatment of seasickness.¹¹ With this drug seasickness occurred one-twentieth as often in a treated as in a control group, and complete relief from seasickness took place within one hour in the thirty-four men who had been used as controls. Favorable results with this drug have also been obtained in the prevention of airsick-

ness,¹² although the effect was not as spectacular as in the case of seasickness. The adult dose is 50 to 100 mg. every five hours. The commonest side effect is drowsiness. Rectal administration may be used in patients unable to retain the capsule when given orally.

REFERENCES

1. Maitland, J. G.: Seasickness, Practitioner 129: 251, 1932.
2. Schwab, R. S.: Chronic Seasickness, U. S. Navy Med. Bull. 40: 923, 1942.
3. Hill, J.: Care of the Seasick, Brit. M. J. 2: 802, 1936.
4. McEachern, D., Morton, G., and Lehman, P.: Seasickness and Other Forms of Motion Sickness, War Med. 2: 410, 1942.
5. Brooks, M.: Seasickness, U. S. Navy Med. Bull. 37: 469, 1939.
6. Poppen, J. R.: Seasickness—Etiology and Treatment, U. S. Navy Med. Bull. 37: 463, 1939.
7. Pflanz, E.: Zur Aetiologie der Seekrankheit, Wien. klin. Wehnschr. 16: 896, 1903.
8. Keevil, J. J.: Seasickness, J. Roy. Nav. Med. Serv. 21: 216, 1935.
9. Desnoes, P. H.: Seasickness, J. A. M. A. 86: 319, 1926.
10. Conn, J. H.: The Play Interview: A Method of Studying Children's Attitudes, Am. J. Dis. Child. 58: 1199, 1939.
11. Gay, L. N., and Carliner, P. E.: The Prevention and Treatment of Motion Sickness, I. Seasickness, Bull. Johns Hopkins Hosp. 84: 470, 1949.
12. Strickland, B. A., and Hahn, G. L.: The Effectiveness of Dramamine in the Prevention of Airsickness, Science 109: 359-1949.

Comments on Current Literature

NEWCASTLE DISEASE

NEWCASTLE disease (avian pneumoencephalitis, avian pseudoplague) is primarily a virus disease of poultry, giving rise to both respiratory and nervous system effects in young birds, and chiefly to respiratory effects in older birds. The disease in fowls was first recognized by Kraneveld in the Dutch East Indies in 1926. During the following year the causative agent was isolated by Doyle¹ at Newcastle-on-Tyne, England. Since that time the disease has been reported in all parts of the world and is now well recognized as an important disease entity in poultry. The natural disease has been observed not only in barnyard fowl, but in pheasants, partridges, sparrows, crows, and parrots.

In a recent article in the *American Journal of Public Health* (June, 1949), Ingalls and Mahoney² report the isolation of the virus of Newcastle disease from two human subjects, the first cases occurring in the United States which have been identified by recovery of the infectious agent. In a survey of the world literature, these authors were able to find only six reports of infection with Newcastle virus in man, and in only two of these reports was any mention made concerning actual recovery of virus. All of the patients reported had shown clinical manifestations of conjunctivitis and swelling of the eyelids, and in the two instances, Newcastle virus was isolated from the tears.

The first patient of the two reported recently by Ingalls and Mahoney owned and tended a flock of chickens known to be infected with the Newcastle virus. Three days after illness was first noted in the flock, this man developed conjunctivitis of the left eye. Gross examination of the eye, three days after onset, revealed edema of the lids, marked hyperemia, and a definite mucopurulent discharge. Exudate recovered from the eye was treated with antibiotics and inoculated into the allantoic cavity of embryonated hens' eggs. By this means an infectious agent was isolated which produced typical signs of Newcastle disease in susceptible cockerels.

The second case reported by Ingalls and Mahoney was that of a junior veterinary student who had performed autopsies on three chickens shown subsequently to be infected with the virus of Newcastle disease. Two days after the young man had handled the birds, redness and swelling of his right eye were noted. Examination by a physician revealed the presence of conjunctivitis of "a granular type involving the palpebral conjunctiva." Conjunctivitis in this patient persisted for one week and disappeared gradually leaving no ill effects. By means of allantoic inoculation, Newcastle virus was isolated from exudate of the eye. Again typical signs of the disease were produced in cockerels, and virus identification was confirmed by hemagglutination, hemagglutination inhibition, and serum neutralization.

While the Newcastle virus eye infection in man seems to be a mild illness requiring only symptomatic treatment and consisting of a superficial conjunctivitis with no corneal involvement, in two of the cases among laboratory workers,³ the conjunctivitis was accompanied by preauricular lymphadenitis, headache, malaise, and chills, but with no significant rise in temperature.

The work reported by Ingalls and Mahoney represents the first isolation in the United States of the virus of Newcastle disease from man. It is of considerable interest that with the improved laboratory techniques now available, accurate etiologic diagnosis of another disease entity is possible.

The isolation from human subjects of the virus of Newcastle disease, primarily a disease of fowl, serves to re-emphasize the importance of the great reservoirs of infection existing in the animal kingdom. Many of these infectious agents are being shown capable of producing disease in man.

RUSSELL J. BLATTNER.

REFERENCES

1. Doyle, T. M.: A Hitherto Unrecorded Disease of Fowls Due to a Filter-Passing Virus, *J. Comp. Path. & Therap.* 40: 144, 1927.
2. Ingalls, W. L., and Mahoney, Ann: Isolation of the Virus of Newcastle Disease From Human Beings, *Am. J. Pub. Health* 39: 737, 1949.
3. Burnet, F. M.: Human Infection With the Virus of Newcastle Disease of Fowls, *M. J. Australia* 2: 313, Oct. 16, 1943.
Anderson, S. G.: A Note on Two Laboratory Infections With the Virus of Newcastle Disease of Fowls, *M. J. Australia* 1: 371, Mar. 16, 1946.

News and Notes

A new use has been found for the mobile decompression chamber, a device built to carry out high-altitude flying tests on airplane pilots. British doctors are now seeking to exploit the low pressure conditions thus obtained in an effort to cure children suffering from whooping cough. In a series of experiments conducted by Dr. H. Stanley of Park Hospital, Hither Green, London, S.E., child patients undergo the sensation of flying at 12,000 feet when the atmospheric pressure in the chamber is gradually lowered. Final results of the new method will take about six months to compile but it is reported that in a Paris hospital the treatment has cut the time of cure from weeks to a few days in 25 per cent of cases. The illustration shows the decompression chamber installed.



The Transactions of the Fifth International Pediatrics Congress held in New York in 1948 may be obtained from Almqvist & Wiksells, Boktryckeri Aktiebolag, Huvudkontoret, Uppsala, Sweden. Price 25 Swedish Crowns.

The following officers have been elected for 1949-1950 by the Section on Pediatrics of the American Medical Association: Chairman, Dr. Margaret Nicholson, Washington, D. C.; Vice-Chairman, Dr. Adolph DeSanctis, New York; Secretary, Dr. Wyman C. C. Cole, Detroit.

Dr. Lee E. Farr, Director of Research at the duPont Institute of the Nemours Foundation, has been appointed Chairman of the Medical Department at the Brookhaven National Laboratory, Upton, L. I.

Pediatric Calendar 1949-1950**American Board of Pediatrics:****Oral Examinations:**

Cleveland	Sept. 16-18, 1949.
New York	Oct. 21-23, 1949.
Chicago	Dec. 9-11, 1949.

American Academy of Pediatrics:

Annual Meeting, San Francisco, Nov. 14-17, 1949.

American Pediatric Society:

Annual Meeting, French Lick, Ind., April 1950.

Society of Pediatric Research:

Annual Meeting, French Lick, Ind., April 1950.

Sixth International Congress of Pediatrics:

Zurich, Switzerland, July 24-28, 1950.

Book Reviews

Juvenile Rheumatism. G. E. M. Scott, Melbourne, 1948, W. Ramsay (Surgical) Pty., Ltd., 163 pages. Price, 25 Shillings.

This short monograph is primarily a review of some of the literature upon rheumatic fever. In addition, the author reports his experiences and observations in treating rheumatic fever at the Children's Hospital in Melbourne, Australia. The comprehensive bibliography which the author has compiled is the chief value of this work. GOLDRING.

Your Child's Mind and Body: A Practical Guide for Parents. Flanders Dunbar, M.D., New York, 1949, Random House, 288 pages. Price \$2.95.

In this book, Dr. Dunbar sets out to answer the "little" questions that arise in the minds of parents who are struggling with the "crises" in personality development during the first six years. These crises are described in terms of disturbances in the areas of sleeping, eating, playing, obedience, and independence. However, the chapters are written in the manner of lectures to medical students, and the bibliography would require the background of the graduate student. The approach is an encyclopedic one, highly intellectualized and somewhat impersonalized. There are lots of rules, illustrated by anecdotes which oversimplify the solution of problems. References to experimental work and psycho-analytical theory add to the impression of superficiality and even glibness.

From the point of view of the reviewer, this book falls into the category of other books about children which the author herself describes as follows: "If you try to correct them (ideas of discipline) by reading books you will probably correct them in a disordered way and feel dissatisfied with yourself and your child because neither you nor he ever understood the real meaning behind the correction or the principle." WARSON.

New Ways in Discipline. Dorothy Walter Baruch, New York, 1949, Whittlesey House, McGraw-Hill Book Company, Inc., 268 pages. Price \$3.00.

Psychiatrists usually shy away from the term "discipline" because of the usual punitive implications which are so contrary to the psychiatric approach of acceptance and understanding. However, there is no denying the social usage and meaning of "discipline" as an important concept in rearing and educating children. Dr. Baruch, from her extensive experience in educational and clinical psychology, is able to effect a compromise between psychiatric and social attitudes which should decrease the confusion of parents and teachers about this difficult topic.

Beginning with the usual dilemma "to spank or not to spank," the author takes the reader behind the scenes and exposes the feelings that motivate the overt behavior which calls for discipline. She then describes simple techniques for eliciting and releasing these feelings. The usual crises encountered in emotional development and their management are gone into in detail as well as the methods of establishing good relationships with children and promoting healthy personality development.

This book is written at the level of the average parent, and obviously for parents. With a great deal of warmth and understanding the author breathes life and feeling into the concept of discipline and describes the meaning of this concept in terms of our modern child guidance approach, which is based on an understanding of the child's emotional needs. Eye-catching headings do not detract from its fluid but well-organized style. In addition to the numerous examples and illustrations, there are twenty line drawings by Lois Fisher which beautifully point up the material.

This book illustrates the fact that very complex subjects can be made to appear quite simple by well-qualified authorities. However, the subject is still complex and parents should be cautioned against demanding too much of themselves and to obtain further help if the methods advocated do not work.

WARSON.

The New York Academy of Medicine. Its First Hundred Years. Philip Van Ingen, M.D., New York, 1949, Columbia University Press, 573 pages. Price \$10.00.

There are only a few local medical organizations in the United States which are national in their influence. The most outstanding example is the New York Academy of Medicine which celebrated its Centennial in 1947. While it has a beautiful home, a library of over a quarter of a million volumes which is second in size to that of the Surgeon-General, and an endowment of over four and a half million dollars obtained gradually over the years, the real importance of the Academy lies in the profound influence it has had on the development of public health, medical education, and medical practice in its own community, and one which has extended to American medicine as a whole. The story of its origin and the growth and expanding development during its "first hundred" years has been told in this volume by Dr. Philip Van Ingen, a well-known pediatrician and former president of the American Pediatric Society and the Academy of Pediatrics. Since his retirement from active practice a few years ago, he has devoted himself to medical history and this splendid volume crowns a distinguished career.

Dr. Van Ingen has chosen to develop the history chronologically by periods marked by the terms of a long line of distinguished physicians who have held the presidency. The early days were not always smooth sledding either financially or scientifically, and the rather acrimonious discussions over medical relationships, ethics, and economics in the early years bring the realization that, relatively speaking, times were as troubled fifty and a hundred years ago as they are today. To the reader it becomes clear that Dr. Abraham Jacobi, the father of American pediatrics, was undoubtedly the most important single figure in the development of the Academy. He was a fellow for sixty years, president from 1885 to 1888, and served as a trustee for twenty-eight years.

The volume is not only of value and of importance as a history of the Academy. As one reads it through, a vivid, clear-cut picture of the development of American medicine as a whole, and the various matters which absorbed the interests and thoughts of medical men from time to time during the last 100 years, is obtained, and thus it becomes a most readable history of the last 100 years of American Medicine. It is well written with many a touch of sly humor. To have worked through the many volumes of records which accumulated over the century, and to select the important ones which really tell the story of the Academy, and on top of this to condense the story into a single interesting, readable volume, was a tremendous task. It is beyond question a most valuable addition to the history of medicine in America, and will be of great interest, not only to those living in New York, who are fortunate enough to be honored by membership in the Academy, but to all who have an interest in the history and development of medicine.

Editor's Column

CERVICAL ARTERIOVENOUS ANASTOMOSIS

MENTAL retardation, cerebral spasticity, and convulsive disorders in children present problems distressing both to the parents of the individual child and to the pediatrician who must rationalize the situation to the parents and encourage them to adjust to their misfortune. Therapy in these conditions has been directed toward training the child in the use of his physiologic nervous residue in the case of retarded or spastic children, and in the use of drugs to suppress and control seizures in children with convulsive disorders.

Elsewhere in this issue appears the description of an operative procedure designed to increase the arterial blood supply to the cerebral cortex through establishment of a cervical arteriovenous fistula, thereby possibly increasing the nutrient and oxygen available to cortical cells with the hope that function of existing cells perhaps rendered abnormal through injury or inflammatory reaction might be improved.

Extensive studies were made of each child before the procedure was recommended, and careful follow-up observations are being made. While the procedure has been employed only since November, 1948, some indications as to its results begin to appear. As of July 1, 1949, eight children with severe convulsive disorders had been subjected to the operation and had been followed long enough to permit some appraisal of possible benefits. Four of the eight children had cessation of episodes following the operation, in two children the number and severity of convulsions were reduced, while in two the procedure seemed ineffective. The observed cessation of convulsive episodes for variable periods following any one of a number of procedures, such as general anesthesia or air injection into the cerebral ventricles, dampens undue enthusiasm for the apparently good results in the cases undergoing the new operative procedure.

Nine children with cerebral spasticity had been similarly observed. In seven, definite improvement occurred, while in two no benefit seemed to have been derived from the procedure.

Eighteen children with severe degrees of mental retardation due to birth injuries or to encephalitic processes had been subjected to the operation. In eleven, distinct improvement was demonstrable, apparently out of proportion to the preoperative rate of development. In seven children, no benefit was apparent. The difficulty of interpreting, objectively, improvement in mental retardation without the lapse of much longer periods of time is recognized.

The procedure, which on first inspection seems to hold promise, must be recognized as a new type of approach to the problem, but requiring extensive trial and particularly a prolonged follow-up period in order that degrees of benefit to be derived may be determined and the types of patients for whom benefit may be expected may be ascertained, also whether early improvement in individual patients will continue so that hopes of parents will not be raised, later to be again destroyed. A procedure offering any likelihood of improving the lot of these children merits thorough but dispassionate appraisal.

C. F. McK.

THE OBJECTIVE OF UNDERGRADUATE MEDICAL EDUCATION

DR. C. SIDNEY BURWELL, who gave the "Annual Oration of the Massachusetts Medical Society" at its recent meeting in May, selected as his subject "Some Responsibilities of Medical Education." It is a most thoughtful and reflective address based on concepts reached during his fourteen-year period as Dean of the Harvard Medical School from which Dr. Burwell retires this year. While he summarizes six major categories of responsibility, of which one or more might be emphasized by different schools, the one of most general interest is his discussion of the instruction leading to the M.D. degree, in which he gives his reflections on the objectives of the undergraduate medical school course. The thing that characterizes present-day medicine, he feels, is the *rapid change* in knowledge and in practice. Harvard, which dates back 167 years, like all other medical schools was founded to prepare men directly for the practice of medicine, and this has been their primary objective over many years. Dean Burwell has come to the conclusion that with the multiplicity of different types and fields of practice, and of other careers open to men with the M.D. degree, the medical school can no longer in its undergraduate course leading to the degree prepare men for entering directly into practice. Rather it must furnish an education during the undergraduate years which will serve as a foundation for future individual development, whether it be some form of specialized practice, research, public health, or administrative duties in the field of medicine. In other words, it must be a *basic course* with emphasis on "an understanding of the mechanism and the natural history of man and his diseases." This, he feels, is the "indispensable objective and duty of medical schools in training physicians for participation in the medicine of the future."

Dean Burwell's remarks bring to a focus a change which has gradually been taking place in many of our medical schools without most teachers fully realizing the change in objective of the instruction which he states so simply and directly. It will take time for most physicians (and even more for the public) to grasp the idea that the objective of instruction in a medical school is no longer one of turning out "practitioners," which has been the objective of medical schools over many generations, provided, of course, that Dr. Burwell's concept of the objective is correct and it becomes the accepted objective. The rapid development of the "American Boards" in the various fields of practice in the last twenty years is, in a sense, an expression of the change in function of the medical school and of the concept of the objective of undergraduate instruction which Dean Burwell puts forward. Incidentally, in another section of the address, Dr. Burwell expresses the fear that the rapid development of the "Boards" and the expansion of their requirements threatens the soundness of advanced training through stereotyped overorganization. This same thought has been expressed by other educators looking on the picture as a whole, and it is a pitfall which the various boards must consider and avoid.

B. S. V.

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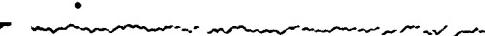


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1 + 1 = 1

To state it another way:

ONE

level tablespoonful
of Pablum (or Pabena)
when mixed with ...

ONE

tablespoonful of milk,
formula or water (hot
or cold) makes ...

ONE

rounded tablespoonful
of cereal feeding of
average consistency.

To make thicker feeding (as in pylorospasm, pyloric stenosis, etc.), increase the amount of Pablum or Pabena. To make thinner feeding, as in 3-months infants, increase amount of milk, formula or water.

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... QUICK AND EASY TO PREPARE ...

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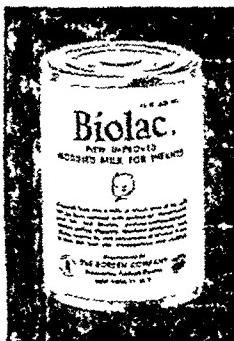
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LESSEN

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SYRUP
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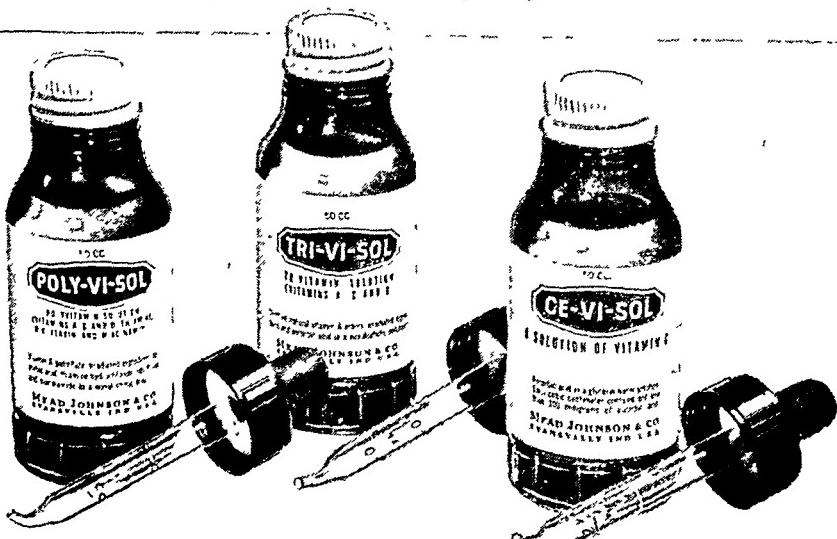
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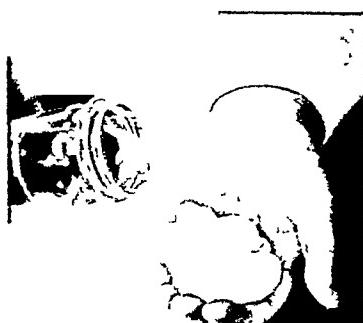
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1. Dieckmann, W. J., and Priddle, H. D.: American J. Obstet. & Gynec. 57:541-546 (March) 1949.
2. Chesley, R. F., and Annitto, J. E.: Bull. Margaret Hague Maternity Hospital 1:68-75 (Sept.) 1948.
3. Healy, J. C.: Journal-Lancet 66:218-221 (July) 1946.
4. Kelly, H. T.: Pennsylvania M. J. 51:999 (June) 1948.



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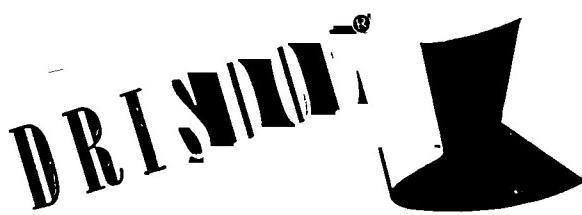


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1. Marriott, W. McK.: *Infant Nutrition*, St. Louis, C. V. Mosby Co., 1941, p. 63.
2. Ibid. p. 96.
3. Kugelmas, J. N.: *Newer Nutrition in Pediatric Practice*, Philadelphia, J. B. Lippincott Co., 1940, p. 653.

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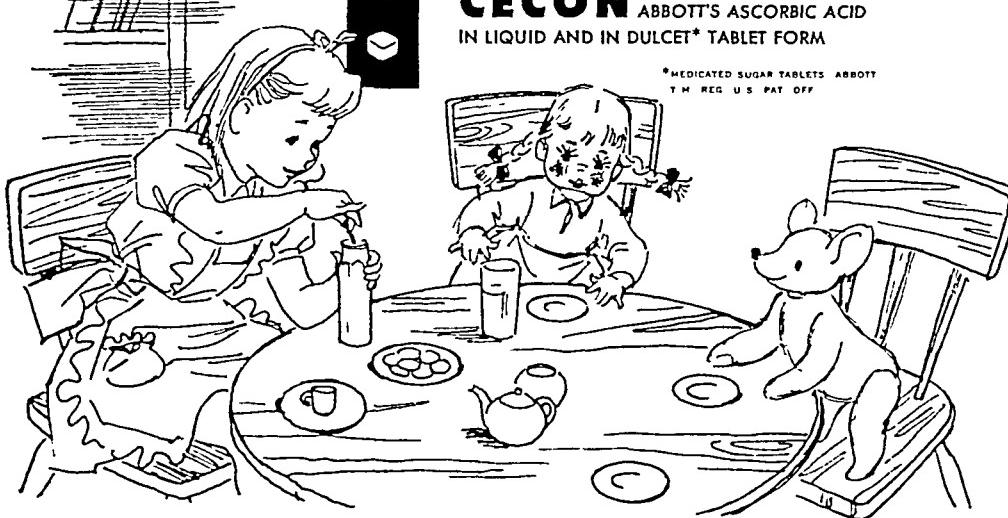
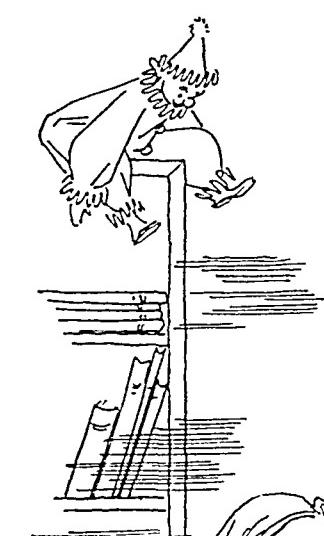
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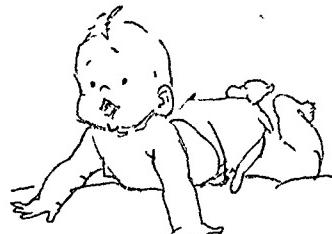
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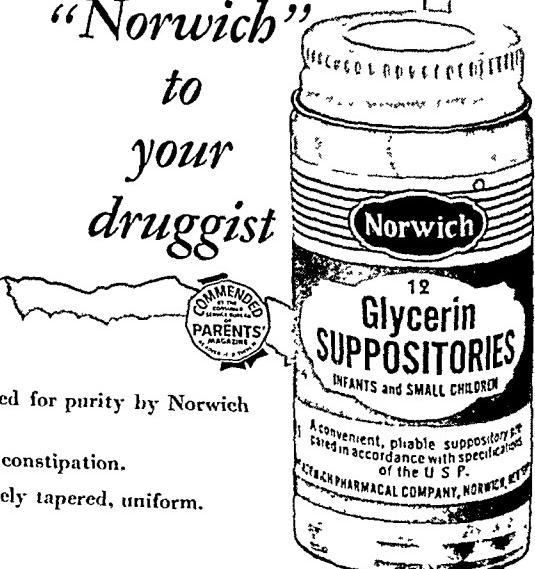
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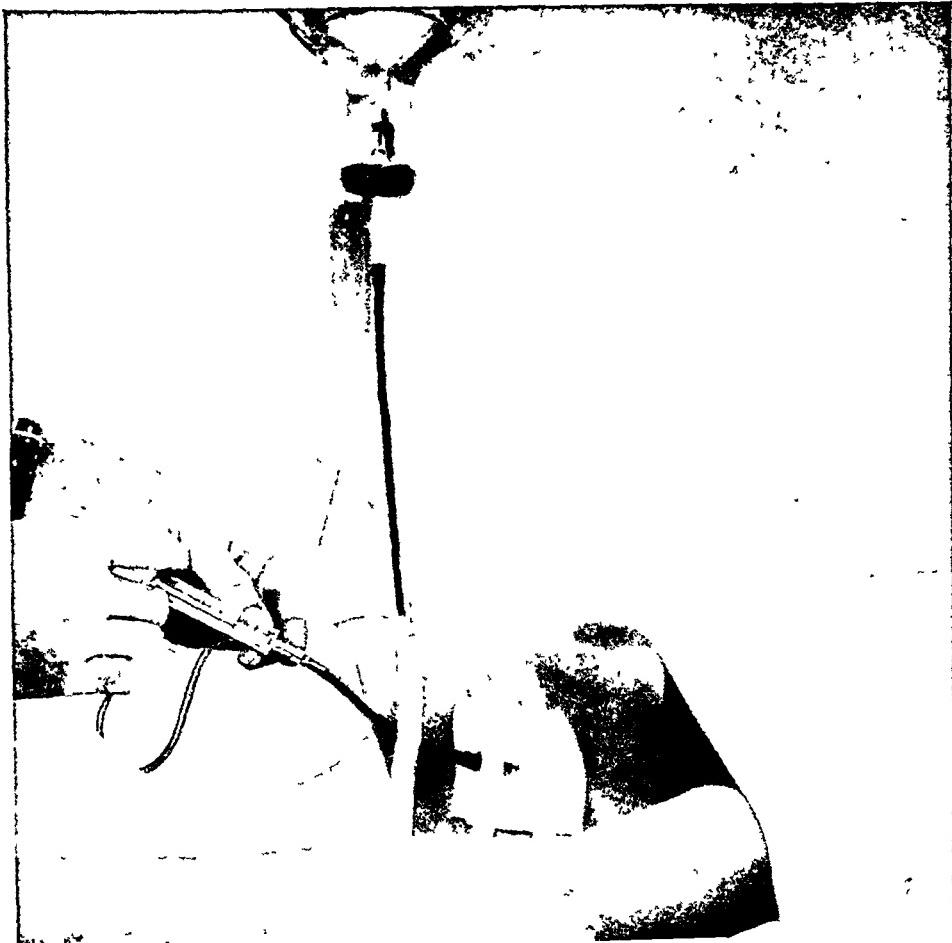
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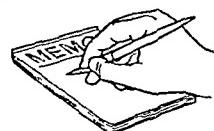
Psychologic Anorexia

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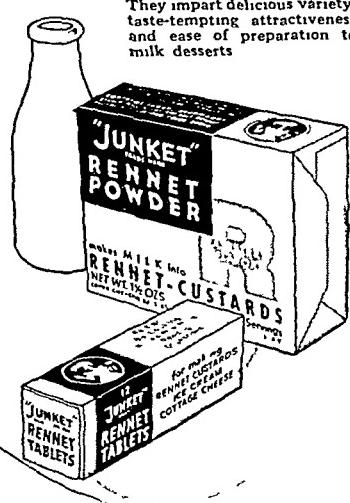
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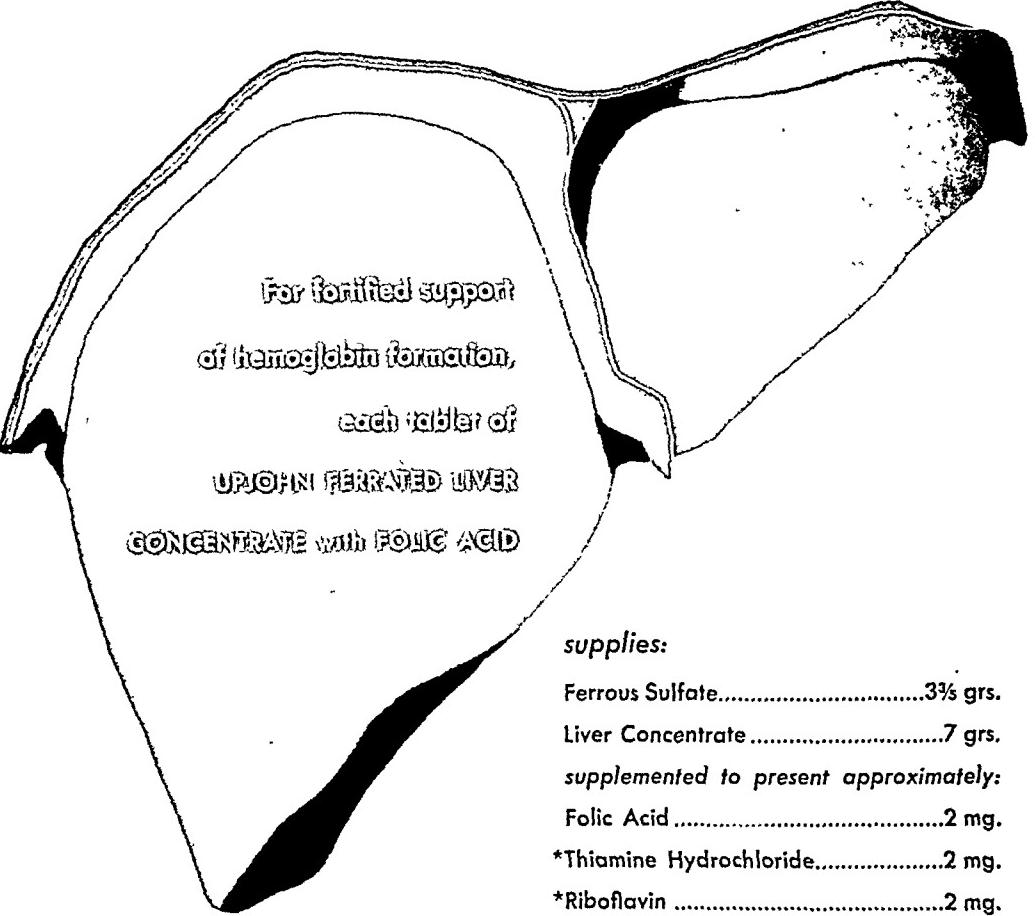


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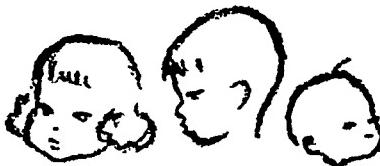
REFERENCES 1 Connell, W. F., et al. Canadian Med Assoc J., 42 220, 1940. 2 Perry, W. F. and Boyd, E. M.: J Pharm Exper Ther., 73 65, 1941. 3 Stevens, M. E. et al. Canadian Med Assoc J., 48 124, 1943. 4 Folts, E. E. et al. J. Lab Clin Med., 28 603, 1943. 5 Graham, B. E.: Ind Eng Chem, Ind Ed., 37 149, 1945. 6 Schulz, F. and Decker, S. Klin Wochschr., 21 674, 1942.

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A valuable aid in the management of specific or non-specific diarrhea, celiac disease and cystic disease of the pancreas.

- *High Calory Diets*

A well tolerated, tasty food concentrate with high, natural vitamin content.

- *Diets of Low Allergenic Content*

A food of naturally low allergenicity which is rendered still more hypo-allergenic by dehydration.

Delicious on cereals, fruits and in milk shakes. The 5½ oz. can contains 20 six inch size bananas costing less than raw fruit.

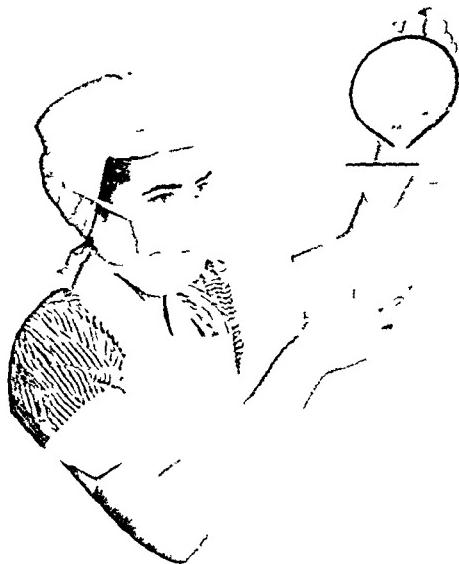


These appetizing golden flakes are sun-ripened bananas, dehydrated at their nutritional peak. Pure banana with nothing added.

December, 1949

send for FREE samples

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Gentlemen: Kindly send me free samples of
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Name _____
Street _____
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Begin in the hospital—continue at home. The natural vitamins A and D daily for about a penny—in drop-dosage for infants, or pleasantly-flavored tablets for older children. Vitamin D wholly derived from cod liver oil, vitamin A adjusted and standardized with fish liver oils.

White Laboratories, Inc.

White's Cod Liver Oil Concentrate LIQUID • TABLETS



What do you demand in a toxoid, Doctor?

*small dosage volume?
purity?*

*concentrated potency?
high antigenicity?*

Of course, doctor, you want the best possible combination of these advantages.

Research and manufacturing know-how of CUTTER, first producer of combined toxoids, have developed in their new purified toxoids products which meet all of your demands.

As an example, consider the superiority of the new, purified DIP-PERT-TET*—for simultaneous immunization against diphtheria, pertussis, and tetanus:

1. Immunization routine is simplified with three injections of 0.5cc each at monthly intervals.

2. Purified toxoids assure virtual freedom from reactions due to bacterial protein components.

3. Alhydrox**—CUTTER'S exclusive adsorbing agent—results in a more solid immunity, fewer post-injection reactions, and less pain on injection.

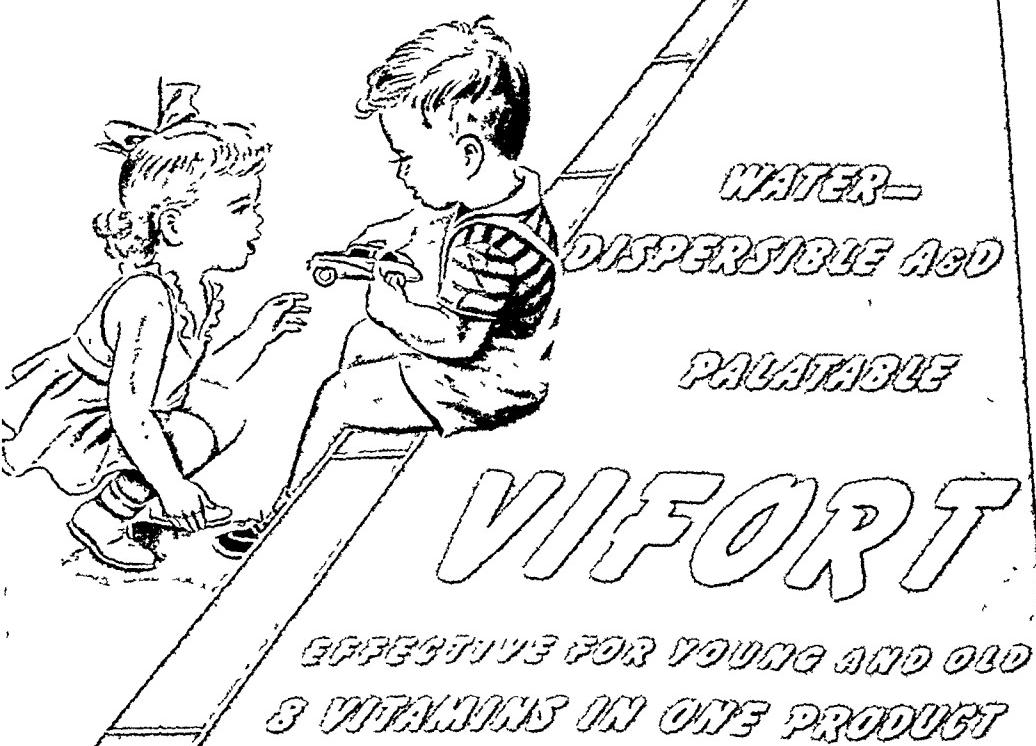
When single immunizations are indicated or booster shots are required, there is a PURIFIED TOXOID—CUTTER—available in both single and multiple dose packages. Your pharmacist has them in stock.

*DIP-PERT-TET—Cutter's diphtheria and tetanus toxoids and pertussis vaccine combined for simultaneous immunization against diphtheria, pertussis, and tetanus

**Alhydrox—Trade name for aluminum alhydrox adsorption, exclusive with CUTTER.

CUTTER

CUTTER LABORATORIES • BERKELEY, CALIFORNIA



WATER-
DISPERSEABLE ACO
PACIFIC

VIFORT

EFFECTIVE FOR YOUNG AND OLD
8 VITAMINS IN ONE PRODUCT

8 VITAMINS IN ONE PRODUCT

Vitamin A
Vitamin D

Thiamine Hydrochloride

Riboflavin

Pantothenic Acid

Niacinamide

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SUGGESTED DAILY VITAMIN REQUIREMENTS

INFANTS, CHILDREN & TEENAGERS

3,000 U.S.P. UNITS

1300 U.S.P. MILS

1 Tsp

1 gm

10 gm

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VIFORT®

polyvitamin drops

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ENDO PRODUCTS INC. • RICHMOND HILL, NEW YORK

The Journal of Pediatrics



For the
well child, for
the sick child,
and for the child
who is neither
sick nor well

ABDEC® DROPS

contain adequate amounts of eight important vitamins in a clear, stable, non-oily and non-alcoholic solution that facilitates rapid absorption and thorough utilization.

Comprehensive multivitamin therapy is thus available

for the well child, as a routine measure to prevent vitamin deficiencies of even minor degree, resulting from common transitory aberrations of eating habits;

for the sick child, particularly during prematurity and anorexic or febrile states, to compensate for diminished intake, decreased absorption or heightened utilization of vitamins;

for the child who is neither sick nor well, where subclinical multiple vitamin deficiencies may be responsible

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ABDEC DROPS are supplied in 15 cc. and 50 cc. bottles with a calibrated dropper for accurate dosage. Each 0.6 cc. (10 minims) contains vitamin A, 5000 units; vitamin D, 1000 units; vitamin B₁, 1 mg.; vitamin B₂, 0.4 mg.; vitamin B₆, 1 mg.; pantothenic acid (as sodium salt), 2 mg.; nicotinamide 5 mg.; vitamin C, 50 mg.

ABDEC DROPS may be placed directly on the tongue or may be added to food or formula. Average daily dose (preferably given at a single feeding) is 0.3 cc. (5 minims) for infants under one year, and 0.6 cc. (10 minims) for older children.

P ARKE, D AVIS & C O M P A N Y

D I T R O I T, 32, M I C H I G A N



incidence of mastitis and other breast complications is reduced with the Plastishield Technic of Aseptic Breast Care.

- Mastitis is frequently the result of excessive handling of breasts and nipples, as well as insufficient cleanliness in postpartum breast care.
- Most cases of mastitis can be traced to nipple fissures or sore nipples which DeLee estimates affect more than half of all lactating women.
- Many breast complications can be avoided when the use of PLASTISHIELDS, begun in the hospital immediately after parturition, is continued at home.
- PLASTISHIELDS are clean, simple to use and comfortably worn.
- They are easily sterilized and prevent soreness, cracking and fissuring of nipples.
- You are invited to write for further information on the PLASTISHIELD Technic of Aseptic Breast Care.

Plastishield technic of aseptic breast care



Bibliography on use of breast shields

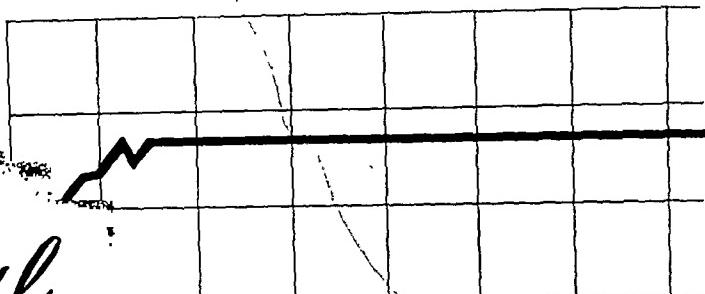
1. Abramson, M.: Breast Feeding the Newborn, Gen Practice Clinics, (Oct.) 1947, p. 318.
2. McKenzie, C. H.: The Use of Plastic Nipple Shields for the Lactating Breast, Journal-Lancet, 65:199 (May) 1948.
3. Hoffert, F.: Simplified Breast Care, The Amer. J. Nurs., 48:372-373 (June) 1948.
4. Thomas, E. C.: The Prevention of Mastitis; the nursing problem, Edinburgh, M. J. 34:456-441, 1947.
5. DeLee, J. B.: Principles and Practice of Obstetrics, W. B. Saunders Co., Phila., 1938.

Plastishield, inc.

MINNEAPOLIS, MINNESOTA

PATENT APPLIED FOR AND TRADEMARK REGISTERED IN THE UNITED STATES

maintain salicylate blood levels



DECO_{Sal}

(DONLEY-EVANS)

In Rheumatic Fever and Arthritis,
therapeutic salicylate blood levels now can be main-
tained without unpleasant side-effects or toxic symptoms.

WITHOUT TOXIC DISTRESS: DECO_{Sal}, a
new salicylamide compound, permits the use of large
doses of salicylates for prolonged and intensive treat-
ment without toxic reaction.

DECO_{Sal} (Donley-Evans) obviates untoward hematic
effects or depression of vitamin C levels; avoids gas-
tric distress; provides dramatic symptomatic relief.

For the first time, DECO_{Sal} provides salicylate in un-
coated tablets and in a clear, palatable elixir . . .
easily administered in fractional doses.

Composition: Each tablet, or 10cc. of Elixir, contains
Salicylamide (4 gr.); Succinic Acid (4 gr.); Ascorbic
Acid (C) (40 mg.).

DECO_{Sal} Elixir in 16-oz. bottles.

DECO_{Sal} Tablets (crush-up, uncoated)
in bottles of 100, 500.

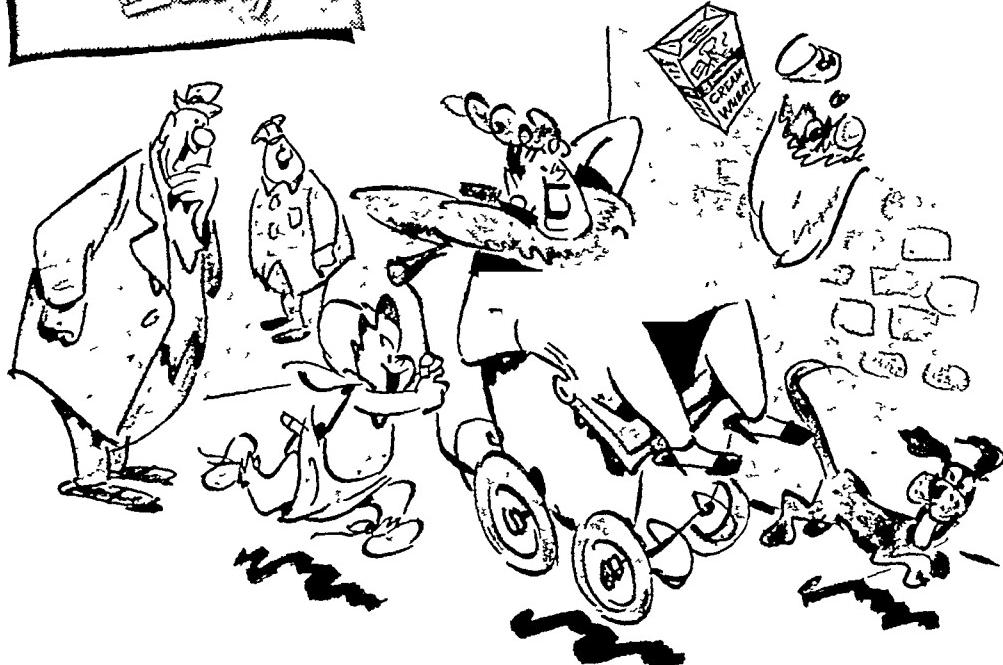
Literature and samples on request.

DONLEY-EVANS & COMPANY



ST. LOUIS 15, MISSOURI

**Is there a doctor
in the house?**



"Help! Junior's got that 'Cream of Wheat' feeling again!"

The "Cream of Wheat" story

in a

Quick facts about America's favorite hot wheat cereal in general diets and special diets for infants, expectant mothers, the aged; and bland diets.

MINERALS. An average serving of Enriched 5 Minute "Cream of Wheat" (20 grams) supplies the full daily minimum requirement of Iron for children under six years of age. It also furnishes 100 mgs. of Calcium and 110 mgs. of Phosphorus.

VITAMINS. An average serving of Enriched 5 Minute "Cream of Wheat" (20 grams) provides whole wheat levels of Vitamin B₁ and also contains Niacin.

PROTEINS. "Cream of Wheat" supplies the good proteins of wheat which, in combination with the excellent proteins of milk, make an important contribution of these essential food elements to the diet.

DIGESTIBILITY. Enriched 5 Minute "Cream of Wheat" cooks to *complete* digestibility—even for infants—in only 5 minutes of boiling (no raw starch, no irritating bran particles).

APPETITE APPEAL. Both Enriched 5 Minute and Regular "Cream of Wheat" have the same satisfying, smooth and delicious wheat flavor that appeals to appetites young and old. Especially tempting to patients with dietary problems.

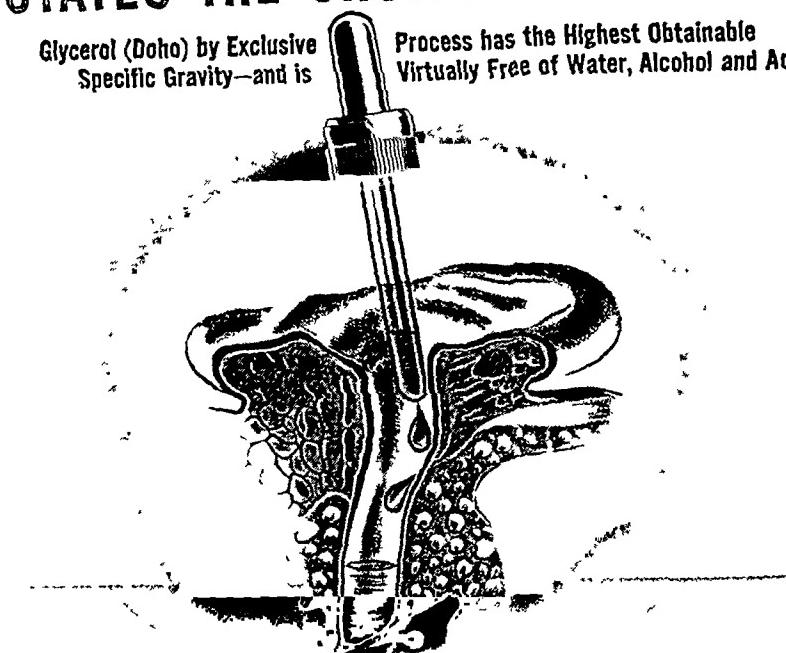
"CREAM OF WHEAT" AND CHEF ARE REG. TRADEMARKS AND REG. U. S. PAT. OFF.



THE INDICATION DICTATES THE CHOICE OF MEDICATION

Glycerol (DOHO) by Exclusive
Specific Gravity—and is

Process has the Highest Obtainable
Virtually Free of Water, Alcohol and Acids



IN ACUTE OTITIS MEDIA

REMOVAL OF IMPACTED CERUMEN

AS AN ADJUNCT TO SYSTEMIC ANTI-
INFECTIVE THERAPY, AS PENICILLIN, ETC.—
CONTAGIOUS DISEASE EAR INVOLVEMENTS

USE

Auralgan

...because its potent decongestant, dehydrating and analgesic action provides quick, efficient relief of pain and inflammation in any intact drum involvement.

FORMULA:

Glycerol (DOHO)	17.93 GRAMS
(Highest obtainable spec. grav.)	
Antipyrine	0.81 GRAMS
Benzocaine	0.21 GRAMS

IN CHRONIC SUPPURATIVE
OTITIS MEDIA, FURUNCULOSIS
AND AURAL DERMATOMYCOSIS

USE

O-TOS-MO-SAN

...a potent chemical combination (not a mere mixture), combining Sulfathiazole and Urea in AURALGAN Glycerol (DOHO) Base—because it exerts a powerful solvent action on protein matter, liquefies and dissolves exuberant granulation tissue, cleanses and deodorizes, and tends to exhilarate normal tissue healing in the effective control of chronic suppurative otitis media.

FORMULA:

Urea	2.0 GRAMS
Sulfathiazole	1.6 GRAMS
Glycerol (DOHO) Base.....	16.4 GRAMS

Literature and samples sent to physicians on request.

DOHO CHEMICAL CORP.—Makers of AURALGAN and O-TOS-MO-SAN NEW YORK 13

External Cod Liver Oil Therapy

D E S I T I N

O I N T M E N T

Contains Crude Cod Liver Oil, Zinc Oxide, Talcum, Petrolatum and Lanolin

Used effectively in GENERAL PRACTICE for the treatment of Wounds, Burns, Indolent Ulcers, Decubitus, Intertrigo, Skin Lesions, Hemorrhoids, Anal Fissures, etc.

In PEDIATRICS for the treatment of Diaper Rash, Exanthema, Chafed and Irritated Skin caused by Urine, Excrements or Friction, Prickly Heat and in the nursery for General Infant Care.

Fatty acids and vitamins are in proper ratio, thereby producing optimum results. Non irritant, acts as an antiphlogistic, allays pain, stimulates granulation, favors epithelization. Under Desitin dressing, necrotic tissue is quickly cast off. Dressing does not adhere to the wound. In tubes 1 oz., 2 oz., 4 oz., and 1 lb. jars.

Desitin Medicinal Dusting Powder is superfatted with crude cod liver oil in a non irritating powder base. Indications: In infant care in the treatment of IRRITATED SKIN, SUPERFICIAL WOUNDS, DECUBITUS, INTERTRIGO, PRURITUS and URTICARIA. In 2 oz. Shaker-Top Cans.

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Samples
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For the Medical Profession

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iron therapy without distress

Youngsters on ordinary iron therapy often feel as if they had swallowed a buzz saw. The nausea, vomiting, gastro-intestinal distress, diarrhea, constipation so often associated with the use of these preparations are eliminated when you prescribe Fergon, stabilized ferrous gluconate. It is usually so well tolerated^{1,2,3} by even your least iron-tolerant little patient that it may be prescribed *before* meals for maximum absorption. Because Fergon is better tolerated, better absorbed, better utilized, it meets the special needs of infants and growing children. Positive iron balance is quickly, pleasantly restored and maintained. Expressly for children—a palatable 5% elixir and 2½ grain tablets.

(1) Teeter, E. J. : *J. A. M. A.*, 127:973, Apr. 14, 1945. (2) Reznikoff, P., and Goebel, W. F. : *Jour. Clin. Investigation*, 16:547, July, 1937. (3) Tompsett, S. L. : *Biochem. Jour.*, 34:959, June, 1940.

Fergon®
ferrous GLUCONATE

Winthrop-Stearns inc.
New York 13, N.Y. Windsor, Ont.

December, 1949

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Page 25

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LOWILA

CAKE * LIQUID

When soap is taboo in DIAPER
RASH and INFANTILE ECZEMAS

LOWILA CAKE for skin cleansing

The only detergent cake which is entirely soapeless yet cleanses as well as soap. No alkali whatsoever, pH approximates normal skin, never irritates. Less slippery than ordinary soap so mother can hold baby more firmly while bathing. Good lather.

LOWILA LIQUID for clothes and household

Washes diapers, bedclothes, infant wear beautifully; soapeless and nonirritant in proper dilution. Does not leave the alkaline, irritating residue left by soaps.



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Convince me with TRIAL SUPPLY and literature
LOWILA cake and liquid

Dr. _____

Address _____

BEGINNER'S LUCK



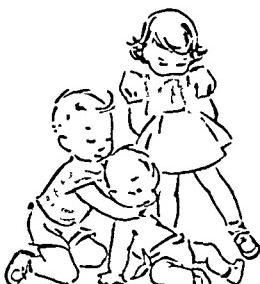
now...



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FOR NEW-BORN PELLERS AND GALS

Beginner's luck indeed—being born in an age that produces such wonderful shoes as BABY JUMPING-JACKS. BABY JUMPING-JACKS are made of the finest, soft and flexible leathers to cuddle and protect young, tender feet. In true JUMPING-JACK tradition these new "first shoes" are quality made and painstakingly finished.



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STAMP
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FROM CRADLE TO SIX MONTHS

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Medical Authorities† Know This Fact:

NO DOCTOR CAN RECOMMEND ANY BETTER EVAPORATED MILK FOR INFANT FEEDING

1. WHITE HOUSE MILK comes exclusively from tested dairy herds.
2. Processing of the milk is rigidly controlled under the most modern and sanitary conditions at the spotless White House Milk plants.
3. Many thorough quality and

laboratory tests are made: before acceptance of the raw milk, at each stage of production, and after sterilization.

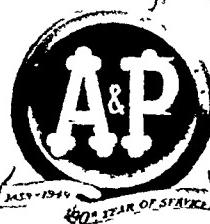
4. Repeated analysis of uniformity, sterility and vitamin D adequacy insure that White House Milk conforms to the very highest quality standards.



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400 U.S.P. Units of Pure Crystalline Vitamin D₃ Per Pint
Satisfaction Guaranteed by A&P or Your Money Back.



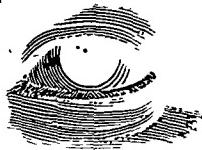
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In a comparison of 12
commonly used antibacterial
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SODIUM SULFACETIMIDE SOLUTION 30%
was found best.

(SODIUM SULAMYD*)



It is "an ideal antiseptic in cases of acute and chronic infection of the conjunctiva."¹ Among 3000 eyes treated "there were no reactions which could be considered either as a sensitivity or as an allergic reaction."¹

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SODIUM SULFACETIMIDE is also available as a 10% NASAL SOLUTION for the relief of nasal congestion in the common cold and for aid in prevention of its secondary complications.

1. Mayer, L. L.: Arch. Ophth. 39:232, 1918.

2. Thygeson, P., in discussion on Mayer, L. L.: Arch. Ophth. 39:232, 1918.

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BACITRACIN-NASAL



More Than Symptomatic Relief IN ACUTE AND CHRONIC SINUSITIS



When dispensed by the pharmacist each cc. of Bacitracin-Nasal-C.S.C. provides: bacitracin 250 units, desoxyephedrine hydrochloride 2.5 mg. (0.25%), sodium benzoate 1%. The solution is stable at refrigerator temperature for 7 days.

Bacitracin-Nasal-C.S.C. is a valuable means of reducing the period of disability when acute sinusitis complicates coryza. Bacitracin, through its specific antibiotic properties, destroys many of the pathogens which flourish in the nose and accessory nasal sinuses. Desoxyephedrine, through its vasoconstrictor influence, improves ventilation and sinus drainage, thus enhancing the action of bacitracin. Bacitracin-Nasal-C.S.C. may be administered by means of a nebulizing spray or by the Parkinson lateral head-low position. Available in $\frac{1}{2}$ ounce bottles on prescription at all pharmacies.

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2. An aqueous solution which does not inhibit ciliary activity.
3. Nonirritant, isotonic.
4. May be administered to both adults and infants.

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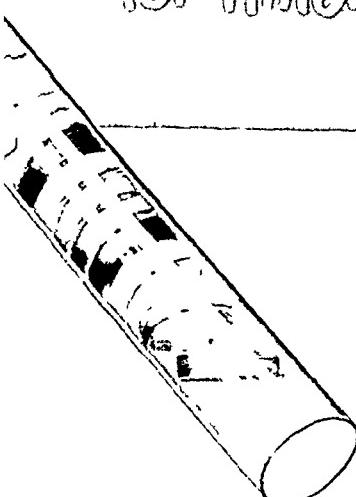
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CONFETS

[FLAVORED TABLETS BUFFERED PENICILLIN SCHENLEY]

For finicky young patients



Each tasty CONFET supplies 50,000 units of crystalline penicillin G potassium buffered with calcium carbonate. These flavored, gaily colored tablets look and taste like candy...make maintenance therapy as welcome as a reward.

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SUPPLIED Glass tubes containing 12 tablets, 50,000 units each, stable at room temperature, no refrigeration required



PINK



WHITE



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Multi-Vi Drops Supply

what the average infant requires

... adequate amounts

of **all** essential

vitamins

White's Multi-Vi Drops

Water Miscible . . .

vitamin D chemically identical
to that of cod liver oil . . .

Non-Alcoholic . . .

Inexpensive . . .

Very palatable . . .



Formula: Each 0.6 cc. contains:

Vitamin A	5000 U.S.P. units
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Thiamine Hydrochloride	1.0 milligram
Riboflavin.	0.4 milligram
Pyridoxine Hydrochloride	1.0 milligram
Sodium Pantothenate	2.0 milligrams
Nicotinamide	10.0 milligrams
Ascorbic Acid	50.0 milligrams

Bottles of 10 cc. and 30 cc.
(with calibrated droppers).

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The Place

Prominent hospitals



The Tests

Jergens Lotion against
usual Hospital Skin Cares

The Results

Jergens Lotion proved
to be the Indicated Care for
Baby Skin



A series of tests of baby skin cares has recently been made in prominent hospitals under the supervision of staff pediatricians. The results are of great interest to the profession.

Jergens Lotion and three treatments commonly used in hospitals were tested on the skins of hundreds of newborn infants. The four treatments tested were:

1. Mineral Oil
2. Soap and Water
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The skins were observed for a period of two weeks for incidence of rashes: macules, papules and pustules.

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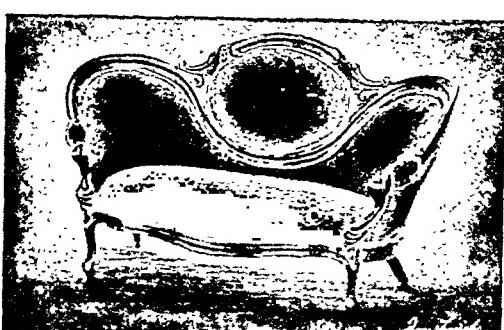
If you have not already received your copy of these Hospital tests, write to the address below and the report will be mailed to you promptly.
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... you wouldn't want to exchange

... comes in so handy on rainy days



... never wears out

... keeps increasing in value

... is so quick and easy to buy
... pleases everyone on your list
AND ... gives itself all over again
(with interest) ten years later?


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against
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Gives the cough relief your patient wants...



In the average case, it's usually possible to control the patient's cough—but often it's a real problem to do it without impairing the cough reflex he needs to keep bronchioles and throat passages clear. That's where you'll find pleasant-tasting Mercodol unique!

For Mercodol contains the cough-controlling narcotic¹ that gives better antitussive action than codeine or heroin, yet keeps beneficial cough reflex . . . a superior bronchodilator² to relax plugged bronchioles . . . an effective expectorant³ to liquefy secretions. And you'll find Mercodol notably free from nausea, constipation, retention of sputum, and cardiovascular and nervous stimulation.

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AN EXEMPT NARCOTIC

The antitussive syrup that controls cough—keeps the cough reflex



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The Journal of Pediatrics



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So, when choosing a food for your baby remember the importance of FLAVOR. Doctors say a baby benefits most from foods he likes and enjoys—and Beech-Nut makes foods that have that appealing flavor.

Babies love them—thrive on them

Beech-Nut **FOODS for BABIES**



A complete line...
to meet the normal
dietary needs of
babies.
Packed in glass.



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and ALL ADVERTISING have been
accepted by the Council on Foods and
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30 days... or life?

During baby's first critical 30 days, a lifetime may be gained or lost—good reason to minimize his burdens and leave him free from the gastrointestinal problems of excessive fermentation, upset digestion and diarrhea, and—good reason for 'Dexin' which has proved an excellent "first carbohydrate." Because of the high dextrin content it is not fermentable by the organisms usually present in the intestinal tract, and undergoes enzymic hydrolysis sufficiently slowly to permit absorption of dextrose about as fast as it is formed. No large quantities of fermentable carbohydrate are likely to be present in the intestine at any one time.

Readily soluble in hot or cold milk, 'Dexin' brand High Dextrin Carbohydrate permits the formation of soft, flocculent, easily digested curds. 'Dexin' does make a difference.

HIGH DEXTRIN CARBOHYDRATE

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Composition—Dextrins 75% • Maltose 24% • Mineral Ash 0.25% • Moisture 0.75% • Available carbohydrate 99% • 115 calories per ounce • 6 level packed tablespoonsfuls equal 1 ounce • Containers of twelve ounces and three pounds • Accepted by the Council on Foods and Nutrition, American Medical Association.
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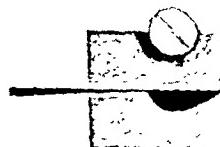
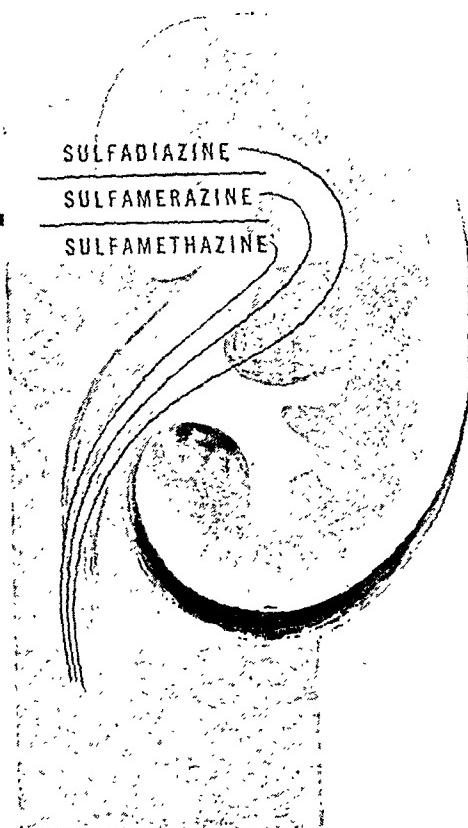
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All three components are absorbed and excreted independently. High blood levels can be maintained without kidney concretion and with minimal sensitivity reactions.

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All three components have a wide antibacterial range and are highly effective in the treatment of pneumonia and other common infections.



0.5 Gm. tablets
Bottles of 100 and 1000
Suspension, 0.5 Gm. per 5 cc.
(pleasant raspberry flavor)
Pint bottles

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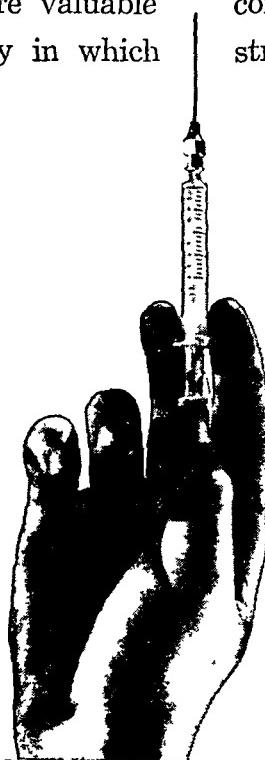
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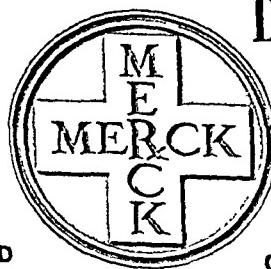
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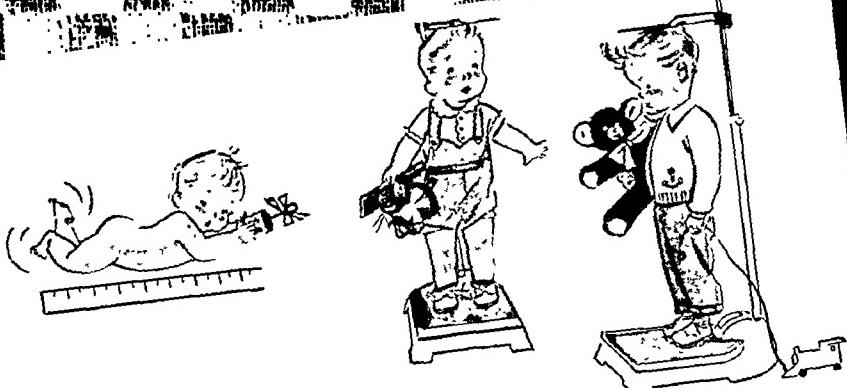
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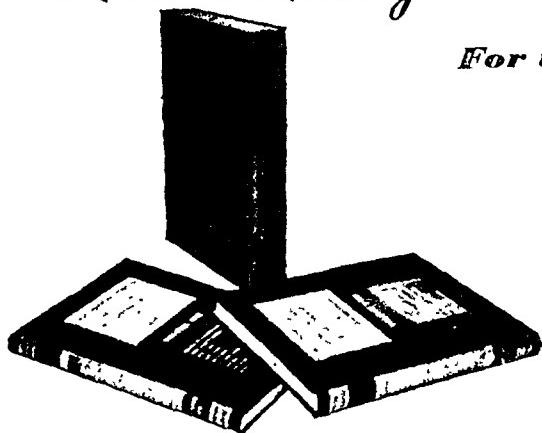
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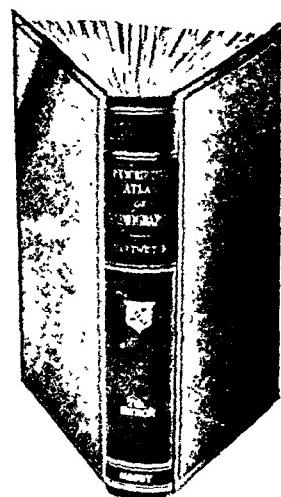
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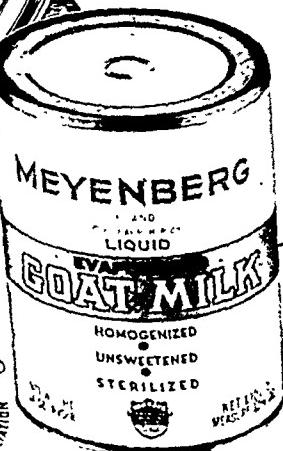
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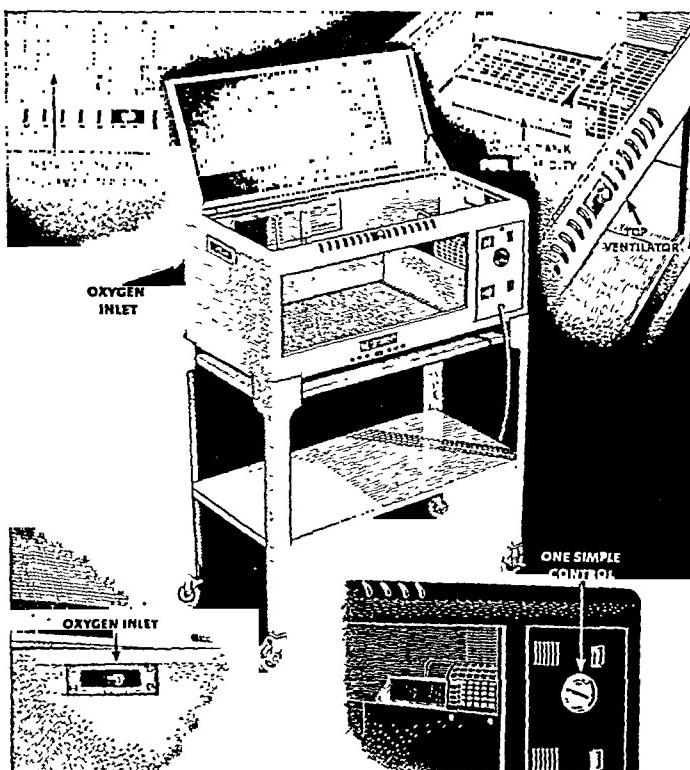


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Original Communications

BRAIN TUMORS IN CHILDREN

I. GENERAL CONSIDERATIONS

A. EARL WALKER, M.D.,* BALTIMORE, MD., AND
THERON L. HOPPLE, M.D., TOLEDO, OHIO

INTRODUCTION

INTRACRANIAL tumors in childhood are now recognized as not infrequent occurrences. The clinical symptomatology, pathologic anatomy, and biologic course of such growths differ from those of brain tumors in adults. This is common knowledge to neurosurgeons but not so well known by physicians in general. Since the life history of these tumors was so clearly presented by Bailey, Buchanan, and Bucy¹ in 1939, certain modifications have been made in their diagnosis and treatment, which warrant a current review of the subject.

This series consists of patients whose symptoms of brain tumor began before their sixteenth birthday. The entire 100 cases presented in this paper have been observed by one of the authors at either the University of Iowa Hospitals, the University of Chicago Clinics, or The Johns Hopkins Hospital. In the majority of cases the patients have been under his treatment, but in a few instances in which operations did not seem advisable, the case came under study at necropsy. The 100 cases in this series have been proved to be tumors by visual verification, and in all but seven instances by histologic examination of biopsy or autopsy tissue. The error introduced by including the few cases which have not been biopsied would seem less than the statistical distortion resulting from their exclusion.

The age distribution curve of tumors in childhood in most series of cases has had an elevation at or about the 5-year age group. In this series one of the highest age incidences (ten cases) occurred in the 6-year-old group. That there is a true peak at this period, probably due to the tendency of medulloblastomas to occur at this age, is demonstrated by the histogram in Fig. 1, in which the age at time of admission to hospital is plotted against frequency. The data is taken from the reported series of brain tumors in children of Bailey and associates,¹ Marburg,⁷ Smith and Fincher,¹³ and the present series.

An analysis of the anatomic location of the tumors in this series confirms the findings of previous writers, namely, that tumors in children occur predominantly beneath the tentorium.^{1, 5, 7, 12}

This work was done while the authors were in the Division of Neurological Surgery, the University of Chicago.

*From the Division of Neurological Surgery, The Johns Hopkins Hospital, Baltimore, Md.

TABLE I.

Hemispherical tumors	19
Third ventricle tumors	20
Cerebellar tumors	45
Tumors of the pons	12
Tumors of the base	4

TABLE II.

Gliomas	78
Meningiomas	5
Epithelial tumors	7
Sarcomas	8
Cysts, congenital	1
Angiomas	1

CASES

80

70

60

50

40

30

20

10

0

0

AGE

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

Fig. 1.—Histogram of frequency of intracranial neoplasms in childhood plotted against age. The data were collected from the series of Bailey and associates,¹ Marburg,² Smith and Fincher,³ and the authors' cases.

The analysis of the tumors on a pathologic basis only emphasizes the fact that gliomas are proportionally more common in children than in adults.

A further breakdown on a combined anatomic and pathologic basis is of value only in indicating the predilection of certain tumors for specific anatomic locations.

<i>Cerebellar Tumors</i>		
Astrocytoma	15	
Medulloblastoma	25	
Ependymal tumor	4	
Glioblastoma	1	
<i>Tumors of the Base</i>		
Sarcoma	3	
Meningioma	1	

<i>Third Ventricle Tumors</i>	20
Pinealoma	1
Epidermoid	1
Glioma	11
Craniopharyngioma	5
Sarcoma	1
Cavum vergae tumor	1
<i>Hemispherical Tumors</i>	19
Glioma	9
Glioblastoma	3
Ependymal tumor	2
Astrocytoma	2
Oligodendrogloma	1
Papilloma	1
Meningioma	4
Sarcoma	4
Epithelial cyst	1
Angioma	1

This breakdown emphasizes the differences between tumors of childhood and adult life. Not only is there a marked predilection for tumors to occur in the posterior fossa, but certain of the tumors of adult life are entirely lacking in childhood. No example of an acoustic neuroma or pituitary adenoma is found in this series, although these tumors constitute almost 25 per cent of the neoplasms of adult life. The meningiomas are only about one-third as common in childhood as in adult life. On the other hand, tumors along the neural axis (medulla, pons, third ventricle) are much more common in childhood than adult life. Moreover, certain of the types of tumor encountered in these regions in adults, such as benign cysts, are rarely seen in children. These peculiarities of brain tumors in childhood have been emphasized by many previous writers.^{1, 3, 7, 13}

GENERAL SYMPTOMATOLOGY

In general, brain tumors in children produce symptoms by reason of intracranial hypertension rather than by their local effect. Minor focal manifestations are likely to be ignored by children. Because of the great compensatory powers of the immature brain, a tumor is often asymptomatic until large enough to produce intracranial hypertension. The majority of neoplasms in childhood are located along the neural axis and early occlude the egress of ventricular fluid, causing an internal hydrocephalus. For these reasons the symptoms of increased intracranial pressure, vomiting and headache, are the most common early manifestations of brain tumors in children.

Vomiting.—The vomiting associated with brain tumors may have no distinguishing characteristics from that due to gastrointestinal disease. Frequently it is not accompanied by nausea and after a violent emesis the patient may sit down and eat a second hearty meal. But at times nausea is intense and persistent. The forceful "projectile" vomiting ascribed to brain tumors is the exception rather than the rule.

It is a curious fact that the vomiting is often precipitated by an illness or a head injury,⁵ perhaps due to the increase of intracranial pressure produced by these conditions. Once begun, the vomiting may stop suddenly for weeks to

start again with or without provocation. Such capriciousness makes the diagnosis of tumor so difficult. Yet with the recognition that vomiting may be the first sign of an intracranial tumor, it is less frequent now that surgeons explore the abdomen for a lesion which lies in the head. But even the neurologist at times finds it difficult to make a positive diagnosis of the cause of so-called "cyclic or functional" vomiting.

Headache.—The headache due to brain tumors in children is not specific. It is often referred to the frontal region. Occipital and suboccipital discomfort is not uncommonly complained of, probably due to distention of the dura mater about the foramen magnum.

Children are usually unable to give a good description of their headache, so that the symptom rarely has reliable localizing significance. Perhaps the most characteristic feature is its occurrence early in the morning. Frequently it wakes the patient or begins on awakening. More often than not it is associated with vomiting, which, strangely, seems to relieve the headache. Aggravation of the headache by stooping, straining at stool, or coughing is rarely noted by children.

Staggering Gait.—The third most common manifestation of a brain tumor in a child is an unsteady gait, unquestionably a corollary of the fact that the neoplasms in this age group are predominantly subtentorial. The difficulty in walking has an insidious onset and is often attributed to weakness resulting from vomiting. But it is more than that. Occasionally it is the prime manifestation of the tumor and at times becomes so severe that the patient cannot stand unassisted.

Convulsions.—Epileptic manifestations are rarely associated with infratentorial tumors¹⁵ but frequently occur with tumors of the cerebral hemispheres. The convulsions differ in no way from those in idiopathic epilepsy, for focal seizures commonly associated with brain tumors also are present in cryptogenic fits. Petit mal attacks, although not unknown, are rarely encountered in brain tumors of children. The majority of the seizures are generalized and may or may not have localizing phenomena. A true Jacksonian march is not common, but convulsions with focal beginnings such as jerking of the face, arm, or leg, are often encountered. Because idiopathic epilepsy is so common in children, such seizures are diagnosed as cryptogenic until the patient develops other neurologic manifestations such as papilledema, paralysis, etc. Occasionally "cerebellar fits" are confused with true convulsions. These attacks of rigid opisthotonus with or without respiratory and cardiac embarrassment are occasionally seen in patients harboring posterior fossa tumors. Only if a detailed account of the attack can be obtained is the differentiation from a grand mal attack possible.

Enlargement of the Head.—In infants and young children whose cranial sutures are not firmly united, enlargement of the head is often the first indication of a brain tumor. The resultant sutural diastasis in many instances may be palpated, or, if slight, recognized by the "cracked-pot" sound produced by percussing the parietal region. Roentgenograms of the skull are particularly

helpful in detecting this phenomenon. In infants the enlargement of the head may lead to the suspicion of a communicating hydrocephalus. Some cases have been so diagnosed only to have a tumor disclosed at necropsy. Subdural hematomas also cause cranial enlargement, but in many cases the head has a peculiar square appearance in contrast to the oval shape of the hydrocephalic head.

Weakness.—A paresis of an extremity, side of the face, or eyelids occasionally is the first sign of a neoplasm. The weakness is usually of extreme value in localization of the neoplasm, especially if generalized intracranial pressure is not present.

Diplopia.—A crossing of the eyes, usually an internal strabismus due to a unilateral or bilateral external rectus weakness, is a common complaint of children with brain tumors. The condition is usually due to tension upon the abducens nerve, and, associated with generalized intracranial pressure, is of no localizing value. Only if the diplopia occurs before intracranial hypertension has developed or if it is associated with other ocular abnormalities such as paresis of conjugate deviation, is it of localizing significance.

Other Symptoms.—Many other complaints are presented by children with brain tumors. Some are the result of intracranial pressure, such as drowsiness; others are due to focal brain involvement and may be of localizing value.

DIAGNOSTIC PROCEDURES

In children it is particularly important to utilize all available diagnostic techniques, for the clinical findings are so often few, nebulous, and sometimes misleading.

Roentgenograms of the Skull.—The routine raying of the skull in antero-posterior and lateral stereoscopic views is a basic necessity in all patients suspected of a brain tumor. Diastasis of the sutures, intracranial calcification, calvarial distortion, or erosion may give a clue to the location of the tumor. Special views of the optic foramen should be taken routinely unless the site of the tumor is obvious on clinical grounds. If the wrist is included on one of the skull views, the epiphysis may be examined for a lead line.

Electroencephalography.—The routine examination of the brain waves often is of localizing value and should be made in all cases. In tumors of the posterior fossa the electroencephalogram may not be of great significance, but occasionally the findings are positive.¹² Its greatest value is in the localization of hemispherical tumors and in the elimination of certain cases of idiopathic epilepsy as tumor suspects.

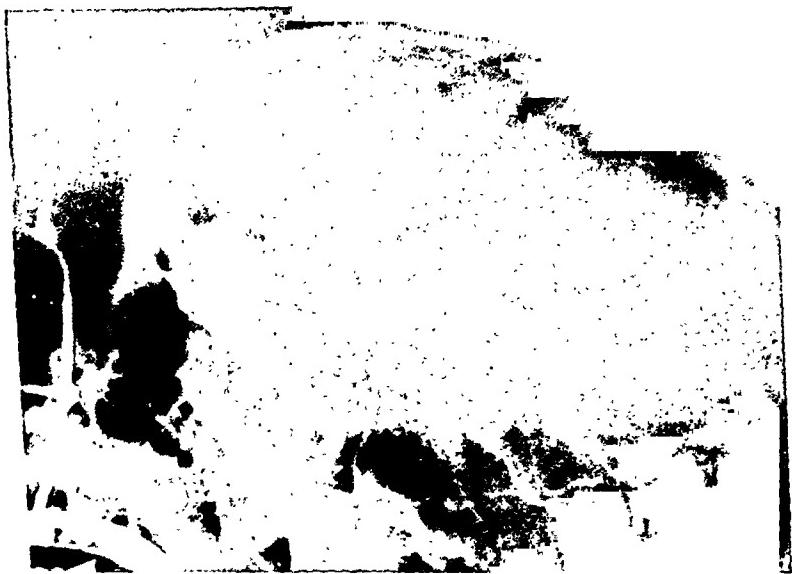
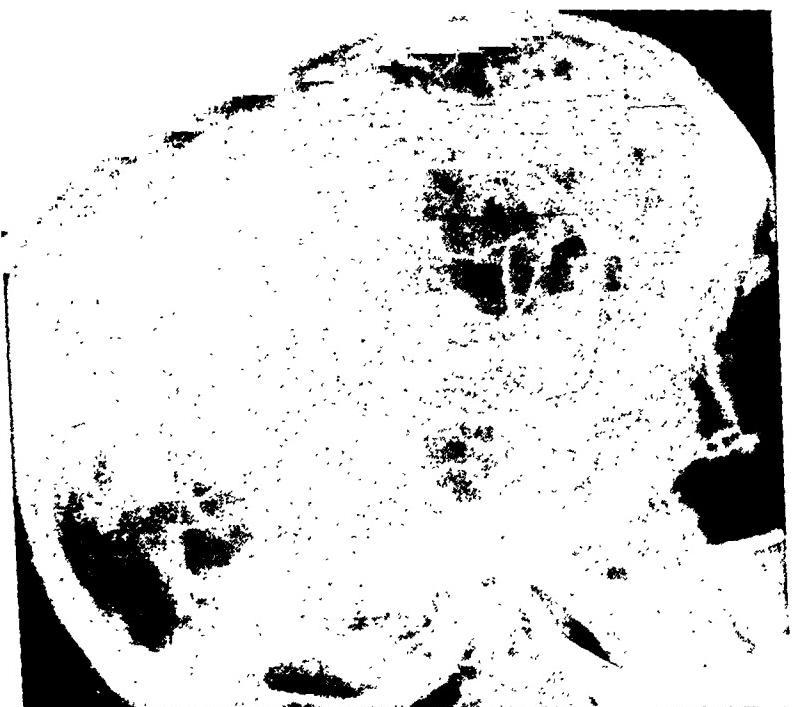
Angiography.—In young children suffering from posterior fossa lesions arteriography is a difficult diagnostic procedure because the vertebral artery is so small and inaccessible. In older children it is possible to puncture percutaneously the common carotid artery and occasionally the vertebral artery. When possible, angiography is of great help in determining not only the location but frequently the type of tumor.

Ventriculography and Pneumoencephalography.—In the absence of clinical evidence of intracranial hypertension, pneumoencephalography is a safe and valuable procedure. It may eliminate the likelihood of a brain tumor or it may



Fig. 2.—*A*, Lateral roentgenogram of the skull with slight sutural diastasis and convoluted markings due to intracranial hypertension. *B*, Lateral roentgenogram of the skull showing intrasellar and suprasellar calcification in a craniopharyngioma.

A.



B.

Fig. 3.—*A*, Lateral angiogram (arterial phase) to show the marked widening of the curve of the anterior cerebral artery due to internal hydrocephalus resulting from a congenital atresia of the aqueduct of Sylvius. *B*, Lateral angiogram showing the distortion of the carotid siphon due to a cranopharyngioma.

brain, the spaces about the sheaths of the cranial nerves, and the subarachnoid space over the hemispheres. It is this fluid which is the prime compensator for increased intracranial mass. This fluid is displaced by the moulding of the cerebral structures into the contour of the skull, first at the site of the tumor,

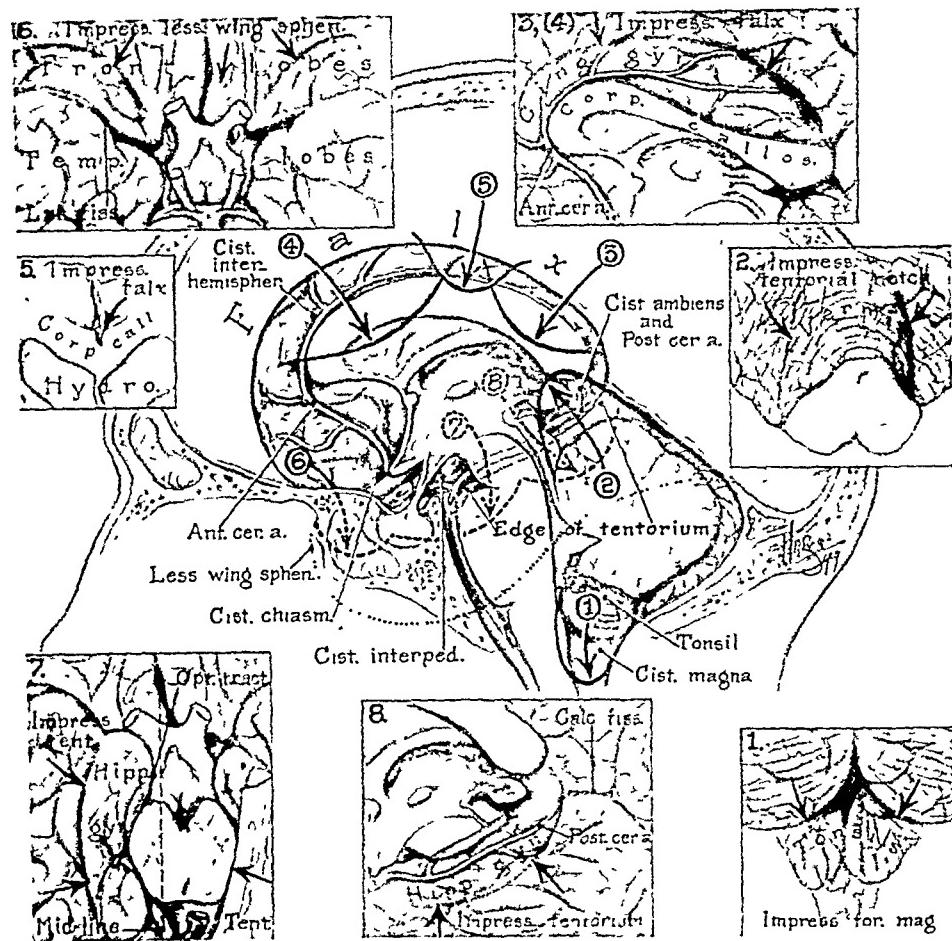


Fig. 6.—Diagrammatic representation of the distortion of the brain resulting from the growth of variously located intracranial neoplasms. The central sketch is a midsagittal section of the brain upon which are superimposed arrows indicating the direction of force exerted by the enlarging tumor. The number accompanying each arrow refers to the insert which illustrates the distortion produced by the particular force.

1, Displacement of the cerebellar tonsils through the foramen magnum, causing the well-known cerebellar pressure cone.

2, Displacement of the anterior lobe of the vermis cerebelli through the tentorial notch due to a posterior fossa tumor.

3 and 4, Displacement of the gyrus cingulum under the tentorium by a parietal or frontal lobe tumor, producing an impression on the cortex of the falx.

5, Elevation of the corpus callosum, often due to an internal hydrocephalus, producing a notching of the superior aspect of the corpus callosum.

6, Displacement of the frontal lobe into the middle cranial fossa and pituitary fossa, usually the result of a frontal lobe tumor. The sphenoidal wing produces an impression on the base of the frontal lobe and the margin of the sella turcica causes a groove across the gyri recti.

7, Displacement of the hippocampus through the tentorial notch with compression of the opposite cerebral peduncle and a groove at the site of the tentorial impression. This is frequently associated with temporal lobe tumors.

8, A slightly more posterior displacement than that in insert 7, often seen with occipital lobe tumors.

later at more distant points. Thus, with a frontal tumor, the frontal lobes are impressed upon the frontal bones, cribriform plate, the tuberculum sellae turcicae and optic nerves, and finally over the edge of the sphenoidal ridge. This process displaces the spinal fluid in the sulci of the frontal lobe, the fluid of the chiasmatic cisterns, and about the pituitary stalk. As a result of this moulding impressions are then seen on the orbital cortex about the olfactory stalks, about the olfactory trigone where herniation occurs into the pituitary fossa over the sharp posterior margin of the tuberculum sellae turcicae, and along the orbital cortex abutting the sylvian fissure. At the same time the frontal horns of the ventricle are compressed, thus decreasing the ventricular fluid.

In the presence of a temporal lobe tumor, the subarachnoid spaces over the temporal lobe are narrowed or obliterated, the sylvian fissure is compressed and pushed upward over the sphenoidal ridge, the pituitary cisterns are displaced, and the subarachnoid space about the brain stem is occluded by the medial margin of the hippocampus, which herniates about the incisura of the tentorium. This causes impressions below the sylvian fissure at the sphenoidal ridge and along the hippocampus. Simultaneously the temporal horn is reduced to a mere slit and the lateral ventricle may be compressed.

In the presence of a parietal lobe tumor, the subarachnoid spaces are narrowed, the ventricles compressed, and the inferior margin of the callosal gyrus often forced under the falx to the other side, thus compressing the subarachnoid space over the corpus callosum. This causes a groove along the callosal gyrus.

In the presence of an occipital lobe tumor the occipital subarachnoid space is compressed, the posterior part of the ventricular system narrowed sometimes to a slit, and the cisterna ambiens obliterated by herniating cortex of the precuneus into the space over the quadrigeminal bodies and about the lateral margin of the mesencephalon. This causes a groove along the precuneus and hippocampal gyrus due to the sharp edge of the tentorium.

In the presence of a posterior fossa tumor the brain stem and cerebellum are moulded into the orifices of exit of the cranial nerves, the foramen magnum, into which the cerebellar tonsils usually herniate, and into the cisterna ambiens, prepontine cistern, and the subarachnoid space about the mesencephalon. This moulding produces the well-known cerebellar pressure cone and a groove about the anterior lobule of the cerebellum due to the pressure against the incisura. The fourth ventricle is compressed and usually distorted.

These are the mechanisms by which the moulding of the brain decreases the amount of spinal and ventricular fluid. At first the changes may be local but as the pressure increases all of the above factors may be operating.

2. Decrease in the Amount of Interstitial Fluid Within the Brain.—Local compression of the brain causes a decrease in the size of the cerebral tissue, probably largely due to loss of interstitial tissue. Obviously the neuronal and neuroglial tissue cannot be eliminated, so that any compression must be the result of decrease in fluids. While some of this may come from the cell, most is probably from the interstitial spaces. That such compression does occur can be demonstrated readily by ventriculograms before and after elimination of a

block causing hydrocephalus. A markedly dilated ventricle before operation may decrease in size to an almost normal sized ventricle within a few weeks after the removal of an obstruction. This decrease in interstitial fluid is probably of extreme importance, for elimination of the cerebral spinal fluid about the brain maximally can only give 40 to 50 c.c. of additional space. Many brain tumors weigh several hundred grams, and dilated cerebral ventricles often contain several hundred cubic centimeters of fluid. The greater part of the space must have come from loss of interstitial fluids.

3. Decrease in the Amount of Intracranial Blood.—The importance of this factor is difficult to assess. That it does play a role is evident from the dilated, tortuous scalp veins frequently seen in cases of brain tumor. The diploic channels are utilized to decrease the amount of blood in the cerebral veins and longitudinal sinus. The arteries are also constricted, as may be seen in arteriograms of hydrocephalus.

This moulding and distortion of the brain as the result of the mass of a brain tumor often produces secondary alterations in the vascular and ventricular fluid systems. The most important of these concerns the changes about the mesencephalon as the result of incisural herniations. Not only may the uncal and hippocampal herniation cause mesencephalic compression, but it may produce narrowing of the aqueduct of Sylvius, resulting in an internal hydrocephalus. Thus the common ventriculographic picture of a temporal lobe tumor is compression of the ipsilateral ventricle and dilatation of the third and contralateral ventricles. This internal hydrocephalus markedly increases the intracranial tension, so that pressure symptoms may rapidly develop.

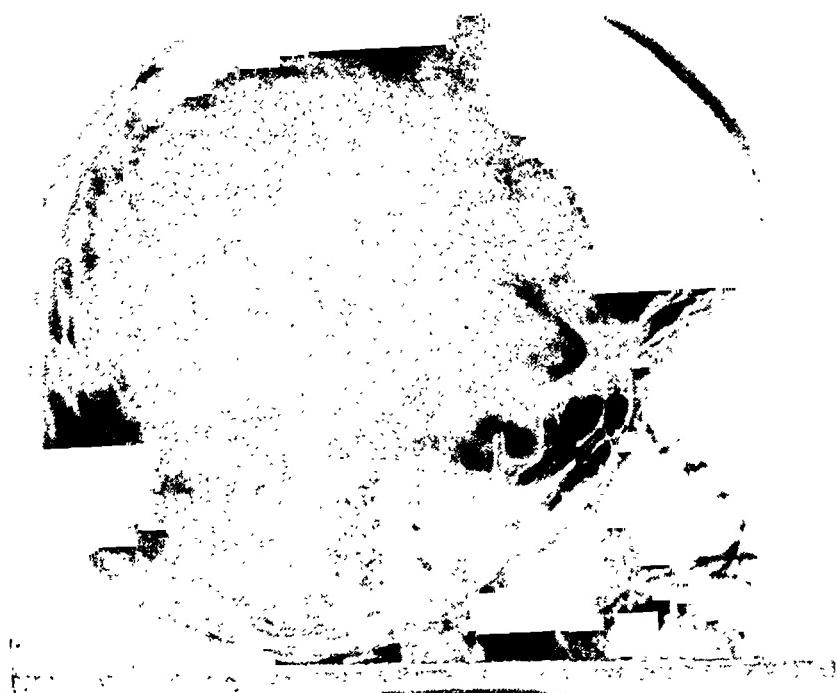
The effect of the tonsillar herniation about the medulla oblongata into the foramen magnum is well known. The effects of the other herniations are not so well recognized. Yet probably herniation through the tentorium is as common with supratentorial lesions as medullary compression by tonsillar herniation with infratentorial tumors. Moreover, uncal herniation may cause compression and thrombosis of the posterior cerebral artery as it passes about the brainstem to enter the calcarine fissure.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of a brain tumor may be divided into two categories, one its differentiation from other diseases and the second its correct anatomic and pathologic designation. The first of these problems is a serious one but one which can be solved correctly in approximately 90 per cent of cases if certain criteria are kept in mind. The conditions which may be confused with a cerebral neoplasm may be classified under the following four headings:

1. Congenital Abnormalities.—Anomalies of the nervous system giving rise to hydrocephalus may simulate tumor, for often a congenital condition does not cause symptoms until some years after birth. The diagnosis of communicating hydrocephalus may be established by dye tests. Congenital atresias of the foramen of Luschka and Magendie give rise to a characteristic high location of the lateral sinuses which is readily recognized in roentgenograms of the skull.

A.



B.



Fig. 7.—Lateral roentgenograms of the skull showing: A, the high position of the lateral sinus and B, the enormously enlarged posterior fossa due to a congenital atresia of the foramina of Luschka and Magendie.

Megalencephaly may occasionally cause a large head but rarely evidences of intracranial hypertension. Congenital atresia of the aqueduct of Sylvius, although rarely producing symptoms in infancy, may not be differentiated from a cerebellar or third ventricle tumor without the aid of air studies.

2. Inflammatory or Toxic Conditions.—Chronic infections of the meninges or brain often cause intracranial hypertension and sometimes focal neurological manifestations. The acute infectious meningitides rarely cause diagnostic difficulty due to the evidences of fever and malaise, but the more chronic meningitides, tuberculous, syphilitic, torula, etc., may occasion some confusion. These conditions are particularly likely to simulate third ventricle tumors. Chronic inflammatory tissue about the medulla may be responsible for an internal hydrocephalus.

Air studies, as well as a spinal fluid examination, may be necessary to eliminate the possibility of one of these chronic infections of the meninges. Serous meningitis, associated at times with middle ear disease, may produce symptoms of a midline cerebellar tumor, but fortunately the condition rarely occurs. An examination of the spinal fluid for a virus may give a positive result, but in most cases a virus cannot be isolated.

Encephalitides may closely resemble a brain tumor. Usually the acute and rather diffuse signs and symptoms of the epidemic, Japanese B, St. Louis, and western equine encephalitis suggest the correct diagnosis. But parasitic infestations such as cystocerosis, echinococcic or hydatid cysts, and schistosomiasis may give rise to localized granulomatous masses. In countries where such conditions are endemic, the possibility of cerebral infection must be considered. Tuberculomas are also common in some lands (England and Chile), where they may constitute as much as one-third of all brain tumors; in this country they are extremely rare, being less than 1 per cent of brain tumors. A purulent encephalitis (brain abscess) may develop without febrile or toxic episode, especially if the primary infection has been treated with penicillin or sulfonamides. Signs of a focal expanding lesion may be the first evidence of its presence.

Of the toxic agents which may cause a clinical picture resembling that of neoplasm, lead is the most important. Roentgenograms of one of the long bones may show deposition of lead at the epiphysis, but this examination may be negative. A chemical determination of the lead level in the blood is the most reliable test.

3. Vascular Disturbances.—The severe vascular disturbances seen in adult life are rarely encountered in children, so that the differential diagnosis between vascular disease and neoplasm is not so important. Occasionally a patient with unrecognized kidney disease will be admitted as a brain tumor suspect, but examination of the blood constituents will suggest the correct diagnosis. Vascular anomalies such as angiomas may give signs of an expanding lesion of the brain. Usually, however, the onset is sudden and regression begins after the initial insult. The presence of a cutaneous nevus or a calcified "worm" intracranially may suggest the diagnosis.

4. Traumatic Lesions.—Subdural hematomas in infants are a common cause of enlargement of the head and convulsions. The diagnosis should be made

easily by a fontanel puncture. In children subdural bleeding is not so common as in adults but one of the authors has encountered a hematoma when doing an intended ventriculography for what was thought to be a brain tumor.

The differential diagnosis of one type of cerebral tumor from another is sometimes much more difficult. In this series several mistakes in localization have been made. Within the posterior fossa it may be difficult, if not impossible, to differentiate a pontine glioma from a cerebellar tumor, even with the aid of air studies.

A 2-year-old boy complaining of vomiting and unsteady gait was found to have normal optic discs, paresis of the third, fifth, ninth, and tenth cranial nerves on both sides and the sixth cranial nerve on the right side, hypotonia and ataxia of all extremities, an unsteady gait, and bilateral Babinski's signs. Because of the extensive cranial nerve involvement, the patient was thought to have a pontine glioma, but at autopsy a medulloblastoma of the cerebellar vermis was found.

A 9-year-old boy complaining of headache and vomiting for four months on examination was found to have nystagmus on looking to the right and left, paresis of the right sixth and seventh cranial nerves, generalized hypotonia, ataxia on the right side, and an unsteady gait. His fundi were normal. His fourth ventricle being well visualized in a ventriculogram, he was considered to have a pontine neoplasm; but on post-mortem examination a cystic cerebellar astrocytoma was found.

These two examples, the most outstanding in the series, must prove that it is impossible to make a consistently accurate pathologic diagnosis on clinical findings. On the basis of these cases it seems wise to explore and biopsy all suspect tumor cases of the posterior fossa.

It is even impossible at times to differentiate a supra- from an infratentorial tumor. A 6-year-old boy complaining of headache and vomiting for three months was found to have two diopters of papilledema, hypotonia, so much ataxia that he was unable to walk, and bilateral Babinski's signs. Preparatory to exploring the posterior fossa the surgeon, in tapping for the left posterior horn, encountered a cyst containing 50 to 60 c.c. of yellow fluid. Subsequently a glioblastoma was found to be in the left occipital and temporal lobes; the cerebellum was normal at autopsy a year later.

DISCUSSION

In most cases a child suffering from a brain tumor consults a physician because of a manifestation of intracranial hypertension such as headache, vomiting or papilledema, or excitatory or paralytic—focal dysfunction—of the brain. The diagnosis of neoplasm must be made on the course of the disease and other conditions which may simulate tumor must be eliminated. When a presumptive diagnosis of tumor has been made, its site and pathologic nature remain to be determined. In the absence of definite focal symptoms or findings, the tumor is likely to be located within the posterior fossa. However, tumors of the third ventricle in children often produce no diencephalic manifestations

and cannot be distinguished clinically from tumors of the posterior fossa. Accordingly, the aid of laboratory tests is essential in making a correct diagnosis in such cases. Roentgenograms of the skull may indicate the locus of a tumor by bony erosion or by calcification. Arteriography is of great assistance without much risk. Air studies are often essential but usually must be followed by an immediate attack upon the tumor. Otherwise, vascular changes within the brain secondary to the altered hydrodynamics may precipitate serious signs of impending disaster. Radioactive isotopes may aid in the localization of the tumor.

Even with every technical aid an accurate anatomical and pathologic diagnosis may not be possible. If there is a reasonable possibility of finding an operable tumor the patient is entitled to an exploration. In the case of posterior fossa and hemispherical tumors a direct exploration seems advisable, but in the case of third ventricle tumors the mortality is so high that palliative procedures are wise. In most cases it is impossible to differentiate tumors of the third ventricle from those of the posterior fossa. Since benign tumors of the third ventricle in children are practically unknown, it has been our policy to explore the posterior fossa in such cases and, if no tumor is found there, to make a Torkildsen ventriculostomy, later giving x-ray therapy. This has lowered the operative mortality of third ventricle tumors and insures that an operable tumor of the cerebellum has not been overlooked.

The high incidence of malignant tumors and tumors along the cerebral axis make the general prognosis of brain tumors in children rather gloomy. But the excellent results achieved in cerebellar astrocytomas and certain cerebral tumors admit of some justifiable optimism.

SUMMARY

1. A series of 100 brain tumors in children is analyzed. A marked predilection for tumors to occur in the posterior fossa is found, as well as a tendency for tumors to develop along the neural axis.

2. Many types of tumor commonly seen in adult life—pituitary adenomas, meningiomas, acoustic neuromas—are rarely if at all seen in childhood.

3. The symptomatology of brain tumors in children is largely due to intracranial hypertension, although occasionally focal manifestations are present.

4. The mass of the tumor within the intracranial cavity is compensated for by a decrease in the amount of cerebrospinal and ventricular fluid, in the amount of interstitial fluid, and in the amount of blood in the intracranial cavity. This is accomplished by a moulding of the brain to fill all nooks and crannies ordinarily occupied by cerebrospinal fluid. Herniation about the mesencephalon or medulla may cause serious depression of vital functions.

5. The differential diagnosis of brain tumors is discussed.

REFERENCES

The literature on brain tumors in children prior to 1939 is admirably collected and discussed in the monograph by Bailey, Buchanan and Bucy,¹ and accordingly is not included here.

1. Bailey, P., Buchanan, D. N., and Bucy, P. C.: *Intracranial Tumors of Infancy and Childhood*, Chicago, 1939, University of Chicago Press.
2. Erickson, T. C., Larson, F., and Gordon, E. S.: Absorption of Radioactive Phosphorus by Glioblastoma Multiforme and Therapeutic Application, *Tr. Am. Neurol. A.* 73: 1948. (In press.)
3. Globus, J. H., Zucker, J. M., and Rubinstein, J. M.: Tumors of Brain in Children and in Adolescents. A Clinical and Anatomic Survey of 92 Verified Cases, *Am. J. Dis. Child.* 65: 604, 1943.
4. Johnson, V. C., and List, C. F.: Ventriculographic Localization of Intracranial Tumors. III. Tumors of the Cerebellum and Fourth Ventricle, *Am. J. Roentgenol.* 43: 346, 1940.
5. Le Beau, J.: La hernie du cervelet au-dessus du tentorium. Diagnostic ventriculographique entre les tumeurs de la partie haute du cervelet et les tumeurs de la partie postérieure du troisième ventricle. Leur voie d'abord chirurgical. *Bull. assoc. d. Méd. de lang. franç. de l'Amérique du Nord. L'unior Méd. du Canada* 73: 243, 1944.
6. Lysholm, E.: Experiences in Ventriculography of Tumors Below the Tentorium, *Brit. J. Radiol.* 19: 437, 1946.
7. Marburg, O.: Some Remarks on Tumors of the Brain in Childhood, *J. Nerv. & Ment. Dis.* 95: 446, 1942.
8. Merwarth, H. R.: Exacerbations and Remissions of Symptoms in Posterior Fossa Tumors of Children, *New York State J. Med.* 46: 2742, 1946.
9. Moore, G. E.: Use of Radioactive Diiodofluorescein in the Diagnosis and Localization of Brain Tumors, *Science* 107: 569, 1948.
10. Moore, G. E., Peyton, W. T., French, L. A., and Walker, W. W.: The Clinical Use of Fluorescein in Neurosurgery: The Localization of Brain Tumors, *J. Neurosurg.* 5: 392, 1948.
11. Portugal, J. R.: Anatomia do III ventriculo e suas alterações nos tumores da fossa cranial posterior O Hospital, Rio de Janeiro, 23: 189, 1945.
12. Rheinberger, M. B., and Davidoff, L. M.: Posterior-fossa Tumors and the Electroencephalogram, *J. Mt. Sinai Hosp.* 9: 734, 1942.
13. Smith, W. A., and Fincher, E. F.: Intracranial Tumors in Children: Preliminary Study of 100 Cases, *South. M. J.* 35: 547, 1942.
14. Silverstone, B., and Solomon, A.: Radioactive Isotopes in the Study of Intracranial Tumors: Preliminary Report of Methods and Results, *Trans. Am. Neurol. A.* 73: 1948. (In press.)
15. Webster, J. E., and Weinberger, L. M.: Convulsions Associated with Tumors of the Cerebellum: Clinical and Pathophysiologic Features, *Arch. Neurol. & Psychiat.* 43: 1163, 1940.

ACUTE LYMPHOCYTIC CHORIOMENINGITIS A STUDY OF TWENTY-ONE CASES

WILLIAM ROY GREEN, M.D., SHREVEPORT, LA., LEWIS K. SWEET, M.D.,
WASHINGTON, D. C., AND ROBERT W. PRICHARD, M.D., BOSTON, MASS.

SINCE the entity of lymphocytic choriomeningitis was separated from Wallgren's classification of acute aseptic meningitis¹ by the work of Armstrong and Lillie,² and of Scott and Rivers,³ there have been about 150 supposed cases of the disease reported in the literature. In reviewing the published reports of these cases, it was found that many of them were presented with the etiological diagnosis having been poorly substantiated. This may have been due to the great difficulty attendant upon all virus studies. Since the diagnosis of this disease can be made finally only by virologic study, it is felt that these incompletely substantiated reports may have led to confusion and inaccuracy in the description of the natural history of the disease in man. In order to define more clearly the clinical picture produced by the disease, we are reporting our experience with twenty-one proved cases of acute lymphocytic choriomeningitis.

These patients were studied on the Communicable Disease Service of the Gallinger Municipal Hospital between July 1, 1938, and June 30, 1948. They include all patients for whom the diagnosis was conclusively established in this ten-year period.

The virus of lymphocytic choriomeningitis has been reported to produce three types of clinical illness in man.⁴ These include grippal or systemic illness without central nervous system involvement, an acute meningitis, and an encephalitis. The milder, grippal, illness has been proved only in laboratory experiments and in workers handling the virus,^{5, 6} and has been established in the general population only by the demonstration of animal protecting antibodies in a considerable number of adults whose history indicated no illness suggestive of meningitis.⁷ No patient with this type of illness has been diagnosed in this hospital in the acute phase, nor have we had any patients in whom the encephalitic form of the disease has been diagnosed with certainty. Our experience includes twenty-one patients in whom an absolute diagnosis of the viral etiology of meningitis has been made. Our discussion will be limited to this one type of illness with which we have had experience.

CLINICAL MANIFESTATIONS

The first patient with this form of the disease was seen at this hospital in 1935 and the case has been reported elsewhere.⁸ Since he was not seen by any of us, he is not included in this report.

The clinical findings in the twenty-one patients included in this study are summarized in Table I. The ages of these twenty-one patients ranged from 6 to 39 years. Four patients were in their first decade, six in their second, three in their third, and eight in their fourth. The distribution according to sex was fourteen females and seven males, a definite preponderance of females which

From the Department of Pediatrics and Communicable Diseases, Gallinger Municipal Hospital, Washington, D. C.

TABLE I. CLINICAL FEATURES OF TWENTY-ONE PATIENTS WITH LYMPHOCYTIC CHORIOMENINGITIS

CASE	SEX	RACE	AGE	ONSET	SYMPTOMS						FINDINGS				MISCELLANEOUS SYMPTOMS AND FINDINGS		
					ANTE- CEDENT	MA- LAISE	ANO- REXIA	HEAD- ACHE	NAUSEA VOMIT- ING	STIFF NECK	SEN- SORIUM	STIFF NECK	KERNIG'S SIGN	BRUDZINSKI'S SIGN	TEMPERATURE MAX. ° F.	DUR. DA.	Cough
1	M	W	38	Sudden	Gripe	+	+	+	+	0	Semicoma	2+	+	103	8	Cough	
2	F	N	14	Insid.*	None	+	+	+	+	+	Semicoma	2+	+	104	10		
3	M	W	31	Insid.	Gripe	+	+	+	+	+	Cloudy	2+	+	101	4	Vertigo, tremor	
4	F	W	21	Insid.	Gripe	+	+	+	+	0	Semicoma	2+	+	103	4	Cough, chest pain	
5	F	N	17	Insid.	Gripe	+	+	+	+	+	Semicoma	2+	+	104	6		
6	M	N	30	Sudden	None	+	+	+	+	0	Cloudy	2+	+	102	3	Photophobia	
7	P	N	23	Sudden	None	+	+	+	+	0	Clear	2+	+	102	5	Photophobia	
8	P	W	15	Sudden	None	+	+	+	+	0	Clear	2+	0	102	6	Insomnia, nervous	
9	P	N	6	Sudden	None	+	+	+	+	0	Clear	1+	+	104	5		
10	F	W	17	Insid.	None	+	+	+	+	0	Semicoma	2+	0	102	6		
11	F	W	33	Insid.	Gripe	+	+	+	+	+	Cloudy	2+	0	99	0	Photophobia	
12	F	N	22	Insid.	Gripe	+	+	+	+	0	Clear	2+	+	102	3	Photophobia	
13	F	N	18	Sudden	None	+	+	+	+	0	Cloudy	2+	+	102	3	Cough	
14	M	N	17	Sudden	None	+	+	+	+	0	Comatose	2+	+	102	7	Photophobia	
15	M	W	34	Sudden	None	+	+	+	+	0	Clear	2+	0	102	1		
16	F	N	39	Insid.	Gripe	+	+	+	+	0	Semicoma	2+	+	103	2		
17	M	N	9	Sudden	None	+	+	+	+	0	Cloudy	2+	0	101	4	Abdominal pain	
18	M	N	6	Insid.	Gripe	+	+	+	+	+	Clear	3+	+	101	2	Photophobia, pneu-	
19	F	W	34	Insid.	Gripe	+	+	+	+	0	Cloudy	3+	+	102	4	monia	
20	M	W	32	Sudden	None	+	+	+	+	0	Cloudy	2+	+	102	3	Bilateral papilledema	
21	F	W	8	Insid.	Gripe	+	+	+	+	0	Semicoma	2+	+	105	5	Lobar pneumonia	

*Insid. = Insidious.

has not been noted before. The four patients under ten years of age were divided equally between the sexes. The preponderance of adult female patients lends support to Armstrong's theory of the mouse reservoir of virus in the transmission of the disease⁹ since adult females probably would have closer contact with mice and their excreta in the home than would males. The racial distribution was eleven Negroes and ten whites which corresponds fairly well with the racial distribution of patients seen in this section of the hospital.

The disease apparently occurs with greatest frequency in the spring and fall of the year, and is definitely less common in the summer. The distribution by months and seasons is as follows:

Jan.	Feb.	Mar.	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
1	1	2	2	3	1	0	1	1	2	5	2
Spring (March, April, May)											7 (4 females, 3 males)
Summer (June, July, August)											2 (1 female, 1 male)
Fall (September, October, November)											8 (6 females, 2 males)
Winter (December, January, February)											4 (3 females, 1 male)

The patients came from many social and economic levels, and from varied types of dwellings, from hovels to middle-class suburban homes. Three of our patients were found to have mice infected with the virus of lymphocytic choriomeningitis in their dwellings, and have been reported by Armstrong and Sweet,¹⁰ and Armstrong, Wallace, and Ross.⁹ Three of our patients came from dwellings on the same street, two in one block separated by one house, and one in the next block. In the apartment of one of these three patients mice infected with the virus were trapped. All three of these patients yielded the virus from their spinal fluid.

Headache was the most common single complaint, and was present in all instances. There was no particular localization, though it was frequently described as being generalized, with some accentuation "behind the eyes." Its intensity is marked. Headache persisted for an average of 12.6 days, the longest being thirty days (two cases), and the shortest three days. This symptom frequently was relieved entirely, though temporarily, by lumbar puncture.

Nausea and vomiting were present on or before admission in sixteen of the twenty-one patients, and in three instances continued after admission to the hospital. It is possible that the decrease in intracranial pressure resulting from the lumbar puncture may have relieved the cause of this symptom in most of the patients.

Photophobia was present in six patients, and persisted after admission for several days. It was not related to the fever, occurring when the patient was afebrile. Funduscopic examination was normal in these patients. The only patient in the series with papilledema did not complain of photophobia.

Under grippal symptoms, we have grouped nonspecific symptoms such as sore throat, malaise, generalized aches and pains, and anorexia. All of our patients complained of feeling bad, and anorexia usually was present at one time or another during the course of the disease. Ten of our patients had definite symptoms of grippe at the onset of their illnesses. Eight of these were treated as such for five or more days before the headache and other complaints

J.M. WM. AGE 31 ACUTE LYMPHOCYTIC CHORIOMENINGITIS

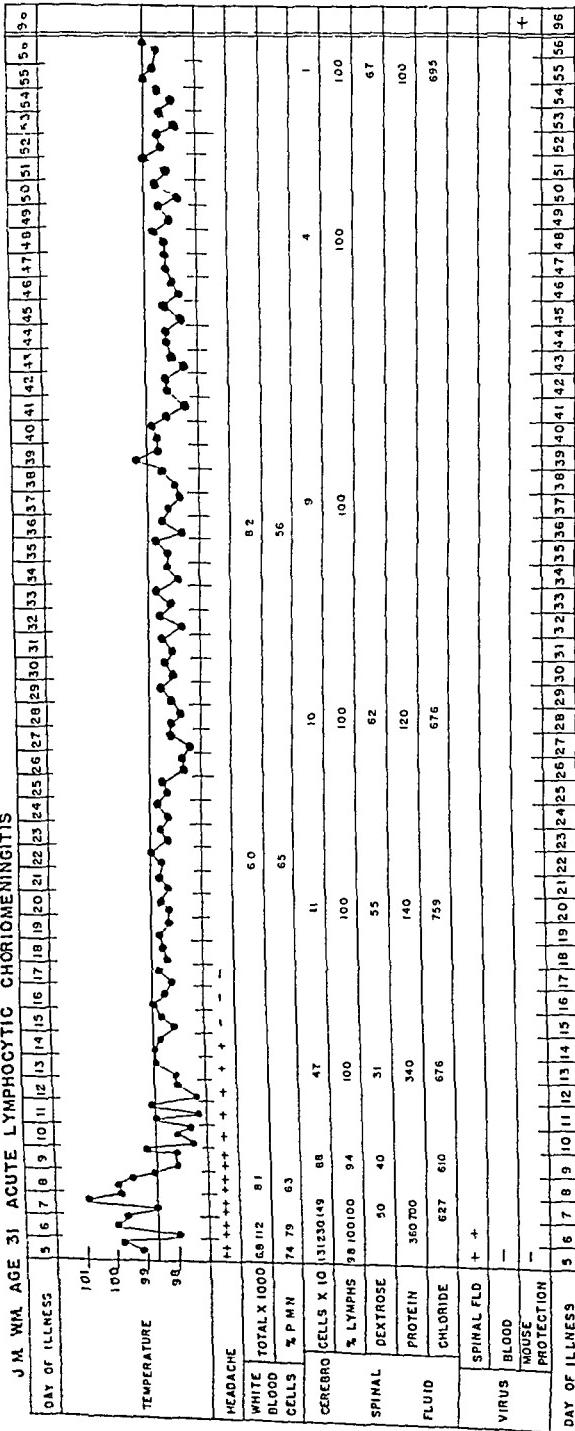


Chart 1.—J.M. (Case 3) became ill five days before entry with headache, fever, vomiting, and pains in the joints and back. His illness became progressively worse until his admission to the hospital. Examination revealed an alert cooperative man who was acutely ill and was complaining of headache. Five days before the onset of his illness, Kernig's and Brudzinski's signs and hyperactive tendon reflexes. His pain was asymptomatic during the remainder of his stay, but remained in bed because of abdominal cramps. He had a stiff neck, positive Kernig's, and positive Brudzinski's signs. His pain was reduced by lumbar puncture, but he remained in bed because of abdominal cramps. The diagnosis of lymphocytic choriomeningitis was confirmed by direct isolation of the virus from the spinal fluid, and by the development of virus-neutralizing antibodies in the blood.

became so severe that hospitalization was sought or recommended. Four of these ten patients had been ill for periods of from one to six months with vague complaints, such as mild headache, weakness, and lassitude. They had been diagnosed as "nervous exhaustion," or "psychoneurosis" by their physicians. Each of the four had an accentuation of their symptoms a few days before admission. Eleven of our patients presented an onset typical of that seen in purulent meningitis. A clear-cut history of sudden appearance of meningeal symptoms, which progressed until hospitalization was sought, was obtained from these patients. About 50 per cent of our patients, therefore, had grippal symptoms before the onset of meningitic involvement.

Fever was present on admission in all patients except one, whose temperature was 99° F. The fever usually was of the sustained variety (Chart 1), disappearing by lysis. The maximum temperature is given for each patient in Table I. During the course of the disease in the hospital the temperatures varied from 100 to 105° F., averaging 102.3° F. The fever persisted for periods of from one to ten days, the average being 4.4 days. The pulse rate was in keeping with the temperature level.

All patients presented stiffness of the neck on admission. The nuchal rigidity was moderately severe, usually being classed as two plus or three plus. The Kernig's and the Brudzinski's signs were positive in sixteen patients.

Of our twenty-one patients, six were rational on admission; the others ranged from "cloudy" to "comatose," in the words of the admitting examiner. One had experienced a convulsion. All appeared acutely ill. Since the word "benign" unfortunately has been incorporated into the nomenclature of this disease, we feel that it is particularly important to stress the severity of the illness that may be seen among these patients.

There were several findings which did not occur with sufficient frequency to be mentioned separately. One patient complained of urinary retention which persisted from the sixth to the eighth day of her illness. Other complaints, each in a single instance, were syncope, vertigo, abdominal pain, tremor, and insomnia.

LABORATORY FINDINGS

The laboratory findings on these patients are presented in Table II.

The spinal fluid findings on the specimen obtained from initial lumbar puncture in each patient are recorded. The patients are arranged in order of descending cerebrospinal fluid cell counts. Lumbar punctures were performed as indicated after admission, but only the significant findings will be discussed here. Specimens of spinal fluid were collected in sterile rubber-stoppered tubes, refrigerated immediately, and sent to the National Institute of Health, Bethesda, Md., as soon as possible for attempts at virus isolation. All spinal fluid cell counts were done immediately on the ward, with and without acetic acid for the removal of erythrocytes. Differential cell counts were performed on the stained smear of the sediment obtained by centrifugation of a portion of the spinal fluid. Dextrose determinations were carried out by two methods. In some instances the five-tube method of Alexander,¹¹ which provides a roughly

quantitative estimation of the sugar level, was done immediately on the ward. The central laboratory performed the standard Folin-Wu¹² type of quantitative determination on freshly drawn fluid.

TABLE II. LABORATORY FINDINGS IN TWENTY-ONE PATIENTS WITH LYMPHOCYTIC CHIROPOMENINGITIS

CASE	ILL	TAP)	CEREBROSPINAL FLUID					BLOOD				
			TEMPERATURE (TIME OF DAYS)	TOTAL CELLS	LYM- PHO- CYTES (%)	PROTEIN	SUGAR	VIRUS	INCREASE IN SERUM ANTIBODY	TOTAL WHITE BLOOD CELLS	POLY- MOR- PHONU- CLEAR- (%)	LYM- PHO- CYTES (%)
1	15	102	3,370	95	405	<10*	+	+	+	9,000	74	25
2	7	104	2,500	99	Pandy 4+	37	+	-(37 days)	5,800	74	24	
3	5	100	2,300	98	360	N†	+	+	6,750	NR‡	NR‡	
4	4	104	2,090	97	NR‡	<10*	+	+	7,650	74	24	
5	7	104	1,550	98	90	N†	+	NR‡	5,600	NR	NR	
6	3	102	1,500	90	211	N†	+	NR	6,400	70	28	
7	5	102	1,350	100	210	40	+	+	8,500	60	29	
8	5	102	1,300	100	Pandy -	50	+	+	4,800	50	46	
9	4	104	1,300	100	NR	N†	+	NR	10,750	42	47	
10	8	102	1,200	90	237	N†	+	NR	8,500	NR	NR	
11	7	99	1,200	90	49	20	+	NR	8,350	38	58	
12	10	103	1,100	90	260	N†	+	+	7,320	60	40	
13	3	102	840	90	88	79	+	NR	5,900	NR	NR	
14	4	102	710	95	112	29	-	+	5,400	NR	NR	
15	10	102	592	100	85	60	-	+	6,200	80	20	
16	14	103	530	100	113	40	+	NR	10,500	NR	NR	
17	2	101	427	90	50	50	-	+	4,100	14	83	
18	7	101	330	95	58	N†	-	+	12,850	54	44	
19	30	102	225	95	131	30	-	+	9,800	NR	NR	
20	2	102	210	90	140	50	+	+	12,000	64	24	
21	2	105	142	100	NR	<10*	-	+	25,800	84	14	

* By qualitative test.

†Normal by qualitative test.

‡NR = No record.

The admission cell count appeared unrelated to the degree of temperature and fell to normal long after the temperature had reached normal limits. The total count on admission varied from 142 cells to 3,370 cells, the average being 1,179 cells. The most striking finding in connection with the cell count was the observation that a high cell count increased the likelihood of isolating a virus from that specimen. Of the fifteen fluids which yielded the virus, only three had cell counts below 1,000, containing 840, 530, and 210 cells, respectively. Also, fluids obtained earlier in the disease are more likely to be virus-containing than later specimens. Eleven of our virus-containing fluids were obtained in the first week of their disease, the remaining four being collected on the eighth, tenth, fourteenth, and fifteenth day of illness, at which time they had high cell counts, 1,200, 1,100, 530, and 3,370, respectively. This finding suggests that the virus may be attached to the cells, and that study of the centrifuged sediment for virus might yield a higher number of positives than the use of all the cerebrospinal fluid.

The name of the disease indicates the usual finding in the differential cell count. The spinal fluid from all our patients contained from 90 to 100 per cent lymphocytes, none lower.

The spinal fluid dextrose at initial and subsequent examinations was normal on all specimens from fourteen patients. Seven patients presented one or more readings with decreased dextrose content (30 mg. per cent or less). Five patients, Cases 4, 11, 14, 19, 21 showed a definite decrease in the initial spinal fluid dextrose as noted in Table II, but were found to have normal spinal fluid dextrose at subsequent examinations. In two patients, extremely interesting decreases in the level of this substance were noted. In one patient (Case 1) the admission spinal fluid contained 3,370 cells, and by qualitative test there was no reduction of Benedict's solution in any of the five tubes indicating a dextrose content of 10 mg. per cent or less. On the following day there was again no dextrose by qualitative test, the cell count being 1,625 at that time. Two days later the cell count was 699, and the dextrose was normal, remaining so on the two following examinations at five- to seven-day intervals. Another patient (Case 13) on admission showed 840 cells, dextrose 79 mg. per cent; four days later her cell count had risen to 2,300 and there was no dextrose by the qualitative test. The following day the absence of dextrose was again demonstrated with a cell count of 1,460. Two days later her cell count was 1,890, her spinal fluid dextrose 50 mg. per cent, her blood sugar 94 mg. per cent. On the two following taps, with cell counts of 340 and 21, normal spinal fluid dextrose was found. Both of these patients (Cases 1 and 13) had the virus isolated from their spinal fluids.

In ten instances out of the sixteen in which protein determinations were done on the initial spinal fluid specimen, the protein value was above 100 mg. per cent. In twelve patients this value was exceeded sometime during the course of the disease. Values ranged from 20 to 700 mg. per cent, and it is worth noting that late in the disease, after the cell count had returned to normal, some patients were found to have a protein level above 100 mg. per cent. Had the latter eases been seen for the first time at this stage, a question might well have been raised as to the cause of such albuminocytologic dissociation. One consequence of the increased protein seen in this disease is the formation of a pellicle, a phenomenon which is evidently still regarded by some practitioners as a sign of tuberculous meningitis. It is hoped that this venerable fear of the really nonspecific pellicle will eventually be dispelled.

In two of our patients the fluid from which the virus was isolated also gave a doubtful, and a weakly positive, reaction, respectively, to a serologic test for syphilis. The specimens giving these reactions also showed a first zone colloidal gold curve of the type commonly called "paretic." Succeeding examinations in both patients revealed normal reactions, the examination being repeated twice again in each case. In the first patient, blood serologies ranged from two plus to four plus, and a competent syphilologist who examined the patient opined that hers might well be a case of a positive reaction due to nonsyphilitic disease. She did not return for the suggested follow-up examinations, and her exact status with regard to syphilis is unknown. The second patient had negative blood serology. These findings suggest that it is possible to obtain a positive reaction to the usual laboratory serological test for syphilis from the spinal fluid of patients with lymphocytic choriomeningitis.

The determination of spinal fluid chlorides was performed only sporadically in our patients, since we feel that little is to be learned from this test on the cerebrospinal fluid. The chloride content of the spinal fluid seems to bear a direct relation to the chloride level in the blood, and it is lowered by any condition affecting the blood chloride level, such as the vomiting and excessive sweating seen in many diseases, especially the meningitides.

The blood picture in fifteen of our twenty-one patients was normal, the white count varied from 4,800 to 10,000, with a normal differential count. Two patients had pneumonia; one had a white blood count of 25,800, the other a count of 12,850 with the usual polymorphonuclear response. Two patients had cervical adenopathy and white blood counts slightly elevated. One 9-year-old boy had a white count of 4,100 with an increase of lymphocytes.

The erythrocyte sedimentation rate was performed on only four of our patients, and all were normal. Farmer and Janeway¹³ raised the interesting point that the sedimentation rate in lymphocytic choriomeningitis is normal, whereas that in tuberculous meningitis is not. We have not had sufficient experience to make any statement on the subject, but feel that further observation is indicated.

Except for traces of albumin during their febrile period, the urines of most of our patients showed nothing remarkable or specific.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The exact diagnosis of lymphocytic choriomeningitis is based on the isolation of the virus from the spinal fluid of patients in the acute stage of the disease, and/or demonstration of an increase in the titer of antibody against the virus following the acute illness in question. Our patients all fulfilled these criteria, fifteen yielding the virus, the remainder showing a definite rise in neutralizing antibody titer. In reviewing the literature on this disease, it was noted that many cases have been presented in which the diagnosis of lymphocytic choriomeningitis was made solely on clinical grounds; usually this diagnosis was appended if no evidence for tuberculosis or syphilis was discovered and the patient recovered. In several reports,¹⁴⁻¹⁶ however, patients diagnosed clinically, without virus isolation, died, and the autopsy findings were presented as those of fatal lymphocytic choriomeningitis.^{14, 15} We feel that reporting of this nature will only confuse the clinical or pathological picture of the disease. We feel that definite demonstration of an etiological agent must be accomplished before it is possible to assign an etiological diagnosis to a disease which varies so slightly from certain other diseases.

The differential diagnosis of lymphocytic choriomeningitis is complicated by the fact that there are a host of conditions that may produce a serous meningitis which is quite similar in clinical manifestations to that caused by the virus of lymphocytic choriomeningitis. Even in the best circumstances the specific diagnoses of those that are due to agents other than syphilis or tuberculosis usually are made with difficulty, if at all. To aid in the differentiation the following outline, with some examples of each, is suggested:

I. Viral

- A. Primary infection of the central nervous system
 - 1. Lymphocytic choriomeningitis
 - 2. Poliomyelitis
 - 3. Encephalitis (various forms)
- B. Secondary infection (associated with rubeola, epidemic parotitis, varicella, rubella, vaccinia, etc.)
- C. Viruses that may invade the central nervous system (herpes simplex, infectious mononucleosis, lymphopathia venerum)

II. Bacterial

- A. Tuberculosis
- B. Infection with *Hemophilus influenzae* (rarely)

III. Spirochetal

- A. Syphilis
- B. Weil's disease

IV. Irritative

- A. Chronic inflammation impinging on the meninges

V. Chemical

- A. Lead poisoning

VI. Fungus

- A. Torula

VII. Protozoa

- A. Toxoplasmosis

VIII. Unknown etiology

- A. Serous meningitis in scarlet fever

In the group of diseases due to viruses, if the season for poliomyelitis is in progress or in view, this disease must be kept in mind until proof of some other etiology is available. Even if a patient is admitted without evidence of the type of paralysis that is characteristic of poliomyelitis he should be examined daily for evidence of muscular weakness. Usually the total cell count in the spinal fluid is lower, and the differential count usually shows not over 70 per cent lymphocytes. In some patients, however, there may be over 90 per cent lymphocytes. The shift from polymorphonuclear cells to lymphocytes, as seen frequently in poliomyelitis, has never been observed in lymphocytic choriomeningitis. The various forms of encephalitis are diagnosed specifically only by virologic study, and present a widely overlapping clinical picture, with signs of diffuse involvement of the central nervous system. The history must be meticulously taken on the subject of exposure to contagious disease. Thus a patient who has no clinical evidence of mumps may have a mumps meningoencephalitis, the etiology of which might go unappreciated if a history of exposure were not obtained. The mumps skin test,¹⁷ and finally, mumps complement fixation antibody determination will establish the diagnosis firmly. In general, serous meningitis associated with the exanthemata and vaccinia is accompanied by a lower cell count than most of the cases of lymphocytic choriomeningitis and is diagnosed by the other manifestations of the disease. Virus infections other than those commonly associated with exanthemata may be present in the central nervous system; for example, infection with the virus of lymphopathia venerum.¹⁸ The virus of herpes simplex, which is widespread in the human

system, rarely invades the central nervous system, and may cause an illness clinically indistinguishable from lymphocytic choriomeningitis. (See below.) As yet unknown is the cause of the central nervous system involvement seen in infectious mononucleosis, where presumptive evidence strongly points to a virus as the etiological agent. The blood picture and the Paul-Bunnell test are of aid here.

Rarely one sees a purulent meningitis that in its early stages may assume a serous form; that is, the pleocytosis in the spinal fluid is predominantly lymphocytic. We have seen *Hemophilus influenzae* meningitis appear in this fashion on several occasions, the diagnosis being made by identification of the organism on smears or cultures of the cerebral spinal fluid.

The differentiation of tuberculous meningitis from lymphocytic choriomeningitis may be extremely difficult. As a rule, the cerebrospinal fluid dextrose is lowered in tuberculosis, but this finding may come late in the disease, and as shown above even relatively persistent reduction of cerebrospinal fluid sugar does not eliminate the possibility of lymphocytic choriomeningitis. The protein and chloride content of the spinal fluid are of little differential value. The total cell count usually is less in tuberculosis, and the differential count usually shows a smaller proportion of lymphocytes. However, the total cell count in tuberculous meningitis frequently numbers well over 200, and the differential count may show over 90 per cent lymphocytes. The definite differentiation of these two conditions can be made most satisfactorily by the demonstration, in patients with tuberculous meningitis, of tubercle bacilli in the spinal fluid, or of tuberculosis elsewhere in the body. Since tuberculous meningitis frequently is a manifestation of hematogenous tuberculosis, the examination of the bone marrow by the technique of Katz, Lifschutz, Milloff, Geiger, and Marshall¹⁹ has proved to be extremely useful in establishing the diagnosis of tuberculous meningitis.

Spirochetal infections usually are diagnosed readily. Serological evidence of syphilis together with a suggestive history will permit diagnosis. Weil's disease is accompanied by icterus which may result in xanthochromia of the spinal fluid. Agglutination reactions are essential in the diagnosis of this disease.

Mastoid disease and brain abscess may produce serous meningitis by irritation of the contiguous meninges, and are revealed by physical examination and localizing neurological signs.

Lead poisoning may produce a chemical meningitis. Typical blood changes and abnormalities in x-rays of the long bones showing a deposition of lead at the growing ends lead to a correct diagnosis. Intrathecal medication, especially with therapeutic sera, will produce a meningeal reaction, as will iodized oil or air which is allowed to enter the cerebrospinal system.

The meningitides due to fungi are poorly understood, with the exception of that due to *Cryptococcus hominis*. Occasionally the cryptococcus may resemble a lymphocyte, and if any suspicion concerning morphology of the cells arises, further test, such as the India ink test, should be done. The investigation of obscure meningitides with cultural methods aimed at fungus isolation is to be recommended if our knowledge of these diseases is to be broadened.

Toxoplasmosis affecting the central nervous system is most frequently seen in infants and is characterized by convulsions and a picture suggestive of encephalitis or hydrocephalus. The spinal fluid may contain from 20 to 2,000 cells. X-ray evidence of calcification inside the skull, with demonstration of agglutinating and complement-fixing antibodies against the toxoplasma organism aid in diagnosis. Examination of the fundi is often of great help in these cases. Serous meningitis²⁰ has been seen in approximately one per cent of patients with scarlet fever at this hospital, the cause being unknown. The meningitis is indicated by the recrudescence of fever after the disease seems to be abating, accompanied by signs of meningeal irritation that often are minimal. It is not related to purulent complications of the disease. The spinal fluid findings are almost identical with those of choriomeningitis, though in general the total cell count is somewhat lower.

After all of the above conditions have been weighed, the etiology is still obscure in a majority of cases; it is for this reason that we do not assign, for recording purposes, the diagnosis of lymphocytic choriomeningitis except when the diagnosis has been established conclusively. Perhaps there are still those who feel that clinical acumen is sufficient to make the diagnosis of lymphocytic choriomeningitis; and indeed, the temptation is strong. We present the following brief abstract for consideration in this regard. This patient, who was seen in this hospital, has been previously reported by Armstrong.²¹

A 15-year-old Negro boy was admitted to the hospital in December complaining of a "cold" for one week, nausea, vomiting and severe headache for twenty-four hours, and semistupor for the twelve hours preceding admission. His only previous hospitalization had been for a "concussion" following an auto accident a year before. Physical examination showed an acutely ill, semi-stuporous Negro boy with a temperature of 101.4° F., pulse 100, blood pressure 140/70. Three plus nuchal rigidity and positive Kernig's and Brudzinski's signs were present and were the only positive findings on physical examination. Spinal fluid examination at this time revealed 900 cells, 96 per cent lymphocytes on stained smear, protein 120 mg. per cent, normal sugar, chlorides, Kahn, and colloidal gold curve; there was no growth on culture in the fluid. A repeat spinal tap was done ten days later, a specimen of the first fluid having been sent to Dr. Armstrong for virus isolation. In the interim the patient's meningeal signs had disappeared by the third day, and his temperature had become normal the fourth day. The second specimen showed 69 cells, 90 per cent lymphocytes, 80 mg. per cent of protein, other normal values. For the next week he remained afebrile, and was discharged after a third lumbar puncture showed 19 cells, all lymphocytes, a protein of 260 mg. per cent, and other normal values. It was felt throughout this boy's illness that he was suffering from lymphocytic meningitis, most probably lymphocytic choriomeningitis caused by the virus of Armstrong and his co-workers. He was signed out as acute lymphocytic meningitis, etiology undetermined.

Final identification of the virus recovered from his spinal fluid showed it to be the virus of herpes simplex.

We have had other patients, especially with mumps meningoencephalitis without parotitis, who have presented an almost identical problem in differential diagnosis.

CLINICAL COURSE AND MANAGEMENT

In nineteen of our twenty-one patients the course of the disease has been short, self-limited, and benign, in the sense that there were no residuals nor any deaths. The average hospital stay for this group of patients was twenty-seven days. The fates of the individual symptoms and signs have been previously discussed. Two of our patients pursued courses that were essentially the same as the others, but developed severe and prolonged headaches, with evidence, on readmission for these complaints, of increased intracranial pressure which required periodic spinal punctures for relief. One man was heard of three years after his initial hospitalization, still unable to work steadily because of his headaches. The second patient who developed this complication was known to have had headaches for several months. He was last heard of three years after his initial hospitalization, complaining of low back pain while in an Army camp; no mention was made of headache at that time. Since he had had a portion of a spinal puncture needle broken off in his paravertebral muscles, with subsequent surgical removal, the back pain cannot be assigned to lymphocytic choriomeningitis. The headaches probably were a result of the meningitis.

F. T. A. N. M., AGE 6 ACUTE LYMPHOCYTIC CHORIOMENINGITIS.

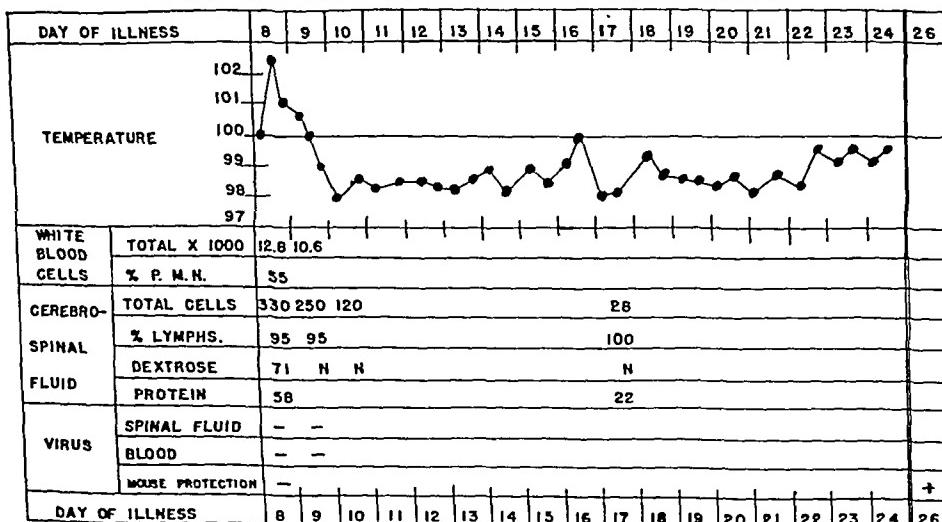


Chart 2.—F.T.A. (Case 18) became ill with headache, stiff neck, anorexia, photophobia, and intermittent fever and vomiting six months before his admission to the hospital. He had vomited with increasing severity during the week before admission. On examination he was a small, poorly developed, apathetic child who was not seriously ill. He showed classical signs of meningeal irritation. Within two days after admission he ceased vomiting and was greatly improved. The diagnosis of lymphocytic choriomeningitis was proved by the fact that he developed virus-neutralizing antibodies in his blood.

The prognosis as to life and aftereffects is excellent. We have seen no deaths in this disease, and complications only as noted.

The treatment of this disease is completely symptomatic, and consists of complete bed rest and analgesics, with fluid and diet control as indicated by the

patient's symptoms and general condition. The most important item is the complete bed rest. The two patients who developed headache, presented above, were among the first patients in our series. Both were allowed to get out of bed when their temperature fell and when they felt as though they would like to get up, at which time their pleocytosis had not subsided. The unfortunate outcome of their cases has led to the policy, perhaps based on coincidence, of keeping patients with meningitis on bed rest in the hospital until the cerebrospinal fluid has receded almost to normal, then to remain in bed at home for four to six weeks following discharge. Since this regime has been enforced we have not encountered any complications in these patients.

Prontosil was reported by Rosenthal, Wooley, and Bauer²² to have a specific effect in inhibiting the production of lymphocytic choriomeningitis in mice when given with the infecting inoculum. Clinical trial of the drug showed that it was without effect in a small series. We have had no experience in its use.

Two patients had pneumonia complicating their disease. They were treated with sulfonamides and responded satisfactorily with no apparent difference from the usual course of such infections.

SUMMARY

1. Twenty-one patients with lymphocytic choriomeningitis are presented. The clinical and laboratory features of the disease are discussed in detail.

2. The differential diagnosis is outlined and the point is emphasized that only a presumptive diagnosis is possible on clinical grounds in this disease, the final proof being the isolation of the virus from the patient's blood or spinal fluid, or the demonstration of an increasing titer of antibody in the patient's blood following the acute illness.

REFERENCES

1. Wallgren, A.: Une Nouvelle Maladie Infectieuse du Septime Nerveum Central, *Acta Pediat.* 4: 158, 1925.
2. Armstrong, C., and Lillie, R. D.: Experimental Lymphocytic Choriomeningitis of Monkeys and Mice Produced by a Virus Encountered in Studies of the 1933 St. Louis Encephalitis Epidemic, *Pub. Health Rep.* 49: 1019, 1934.
3. Scott, T. F. McNair, and Rivers, T. M.: Meningitis in Man Caused by a Filterable Virus (2 Cases), *J. Exper. Med.* 63: 397, 1936.
4. Armstrong, C.: Some Recent Research in the Field of Neurotrophic Viruses With Special Reference to Lymphocytic Choriomeningitis and Herpes Simplex, *Mil. Surgeon* 91: 129, 1942.
5. Armstrong, C., and Hornebrook, J. W.: Choriomeningitis Virus Infection Without Central Nervous System Manifestation (Case Report), *Pub. Health Rep.* 56: 907, 1941.
6. Hoyes, G. S., and Hartman, T. L.: Lymphocytic Choriomeningitis. Report of Lab Infection, *Bull. Johns Hopkins Hosp.* 73: 275, 1943.
7. Armstrong, Chas., and Wooley, J. G.: Benign Lymphocytic Choriomeningitis, *J. A. M. A.* 109: 410, 1937.
8. Armstrong, Chas.: Benign Lymphocytic Choriomeningitis, *Pub. Health Rep.* 50: 831, 1935.
9. Armstrong, C., Wallace, J. J., and Ross, Louis: Gray Mice, *Mus Musculus*, A Reservoir for the Infection, *Pub. Health Rep.* 55: 1222, 1940.
10. Armstrong, C., and Sweet, L. K.: Lymphocytic Choriomeningitis, *Pub. Health Rep.* 54: 673, 1939.
11. Alexander, H. E., Ellis, C., and Leedy, G.: Treatment of Type Specific Hemophilus Influenzae Infections in Infancy and Childhood, *J. PEDAT.* 20: 673, 1942.
12. Kolmer, John A., and Boerner, Fred: Approved Laboratory Technic, ed. 4, New York, 1945, D. Appleton Century Co., page 284.

13. Farmer, T. W., and Janeway, C. A.: Infections With the Virus of Lymphocytic Choriomeningitis, *Medicine* 21: 1, 1942.
14. Baker, A. B.: Chronic Lymphocytic Choriomeningitis, *J. Neuropath. & Exper. Neurol.* 6: 253, 1947.
15. Howard, Marion E.: Infection With the Virus of Choriomeningitis in Man, *Yale J. Biol. & Med.* 13: 161, 1940.
16. Machella, T. E., Weinberger, L. M., and Lippincott, S. W.: Lymphocytic Choriomeningitis. Report of a Fatal Case With Autopsy Findings, *Am. J. M. Sc.* 197: 617, 1939.
17. Habel, Karl: Cultivation of Mumps Virus in the Developing Chick Embryo and Its Application to Studies of Immunity to Mumps in Man, *Pub. Health Rep.* 60: 201, 1945.
18. Sabin, Albert B., and Aring, Charles D.: Meningoencephalitis in Man Caused by the Virus of Lymphogranuloma Venereum, *J. A. M. A.* 120: 1376, 1942.
19. Katz, Sol., Lifschutz, Seymour, Milloff, Bernard, Geiger, Jason, and Marshall, Edward: Unpublished data.
20. Sweet, L. K.: Acute Serous Meningitis and Encephalitis Complicating Scarlet Fever, *Pediatrics* 3: 442, 1949.
21. Armstrong, Charles: Herpes Simplex Virus Recovered From the Spinal Fluid of a Suspected Case of Lymphocytic Choriomeningitis, *Pub. Health. Rep.* 58: 16, 1943.
22. Rosenthal, S. M., Wooley, J. G., and Bauer, H.: Studies in Chemotherapy. The Chemotherapy of Choriomeningitis Virus Infections With Sulfonamide Compounds, *Pub. Health Rep.* 52: 11, 1937.

OBSERVATIONS ON THE TREATMENT OF A CASE OF GLYCOGEN STORAGE DISEASE

GEORGE H. LOWREY, M.D., AND JAMES L. WILSON, M.D.
ANN ARBOR, MICH.

THE treatment of the hepatic form of glycogen storage disease has been unsatisfactory since the establishment of that condition as an entity by von Gierke in 1929. Many methods of therapy have been attempted but few, if any, have resulted in benefit to the patient. We recently have had the opportunity to observe a boy with this disease over a fairly long period of time. Treatment while under our care has consisted of a high protein and low carbohydrate food intake. The symptomatic response of the child to these dietary measures was so satisfactory that we believe the results are worth reporting.

No attempt will be made to give a general review of the nature of the disease as this has been well done by others.¹⁻⁵ A summary of some of the important clinical factors for the purpose of orientation seems pertinent to the present discussion. Glycogen storage disease is a disorder of carbohydrate metabolism in which excessive deposition of glycogen occurs in certain tissues. Either because of abnormal stability of the glycogen, or more probably, because of some disturbance in the enzyme system concerned with its metabolism, this glycogen once deposited becomes extremely resistant to mobilization. Two distinct types of the disease have been described, one involving the liver and the other the heart. Coexistence of the two types is not known to occur. Other organs or organ systems may be involved, particularly excessive deposits may be found in skeletal muscle and kidney, but rarely to such a degree as to cause marked clinical symptoms.¹⁻³ Diagnosis of the hepatic type depends upon the following findings: hepatomegaly, rapid development of hypoglycemia and ketonuria when food is withheld, a subnormal or absent response of the blood sugar to injection of epinephrine, and the demonstration of abnormally large quantities of glycogen in the liver. Valuable confirmatory evidence may be obtained if it can be shown by *in vitro* studies that the liver glycogen is unusually stable.^{3, 4} The glycogen content of the blood has been found to be elevated in all cases where such a determination has been carried out.^{4, 5, 7} Lipemia may be present early in the disease.^{2-4, 6} A bleeding tendency due to lowered prothrombin is often observed. Failure of growth and physical development are common. The condition probably begins in utero but may not be apparent until several months after birth when an enlarged liver is first noted. Episodes of hypoglycemia with weakness, vomiting, and convulsions may be the first symptoms that bring the attention of the parents to the abnormal condition.

The etiology of the condition remains obscure. Heredity plays a prominent role in a small percentage of cases.^{3-5, 12} Humphreys and Kato¹³ suggested that there is an abnormal persistence of fetal behavior of tissues. In support of this

contention they state that fetal and infantile tissues have a high glycogen content, and further, that carbohydrate mobilization from these established depots is poor in the young infant. The possibility that some endocrine dysfunction exists in these patients, as suggested by some investigators,^{1, 17} is not well substantiated in the light of our present knowledge.

Crawford⁵ was able to collect a total of fifty cases of the hepatic form of von Gierke's disease from the available literature to 1946. Others have reported a much larger number,^{1, 13} but it is doubtful that all of these were true examples of this condition. Other diseases which may cause confusion in the differential diagnosis are extreme fatty infiltration of the liver,¹⁴ galactosemia which is often associated with hepatomegaly,^{15, 16} and cirrhosis of the liver. Any of these three conditions may cause hepatomegaly with signs or symptoms of hypoglycemia. A failure of response of the blood sugar to epinephrine injections like that found in von Gierke's disease may be present. However, a persistent ketonuria is not common to any of the three. The demonstration of galactosuria is confirmatory evidence of galactosemia. Finally, liver biopsy will prove the diagnosis if special studies are carried out to demonstrate the presence of abnormally large quantities of glycogen and the absence of fatty infiltration or cirrhotic changes. Other forms of hepatomegaly in children are usually easily differentiated.

REPORT OF A CASE

R. M. was first seen at the University Hospital, Jan. 12, 1948, at the age of 2 years and 2 months. His mother, a graduate nurse, gave a reliable history of the boy's progress up to that time.

He was the result of a full-time pregnancy and weighed 8 pounds at birth. It was noted that he had a large abdomen at birth but for some time thereafter this was thought to be due to the large amount of food ingested. He was breast fed for two months, but during this entire time a supplementary formula of evaporated milk with added carbohydrate was offered and taken. He was apparently well for the first three or four months of life. After this time it was first noted that if he "slept through" his night bottle he would experience mild, generalized, clonic convulsions early in the morning. They rarely lasted more than a minute or two and always stopped after formula was given. He frequently vomited a portion of his first morning feeding. No vomiting occurred later in the day. When the intervals between feedings were shortened neither of these symptoms appeared, with few exceptions, until the child was about 10 months of age. With the increased activity that the patient showed at this age the convulsions again became prominent, occasionally occurring as often as two to three times a day, but most severe in the early morning before the first feeding. At this time he was put on a high carbohydrate diet of three meals a day plus frequent feedings between meals and always a late night feeding. At the time the patient was admitted to this hospital an average day's consumption consisted of about 1,300 to 1,400 calories of which more than 60 per cent was carbohydrate and about 25 per cent was protein. On this regimen he would have periods as long as two months without convulsions. In addition to treatment by diet the boy had received short courses of thyroid and pitressin therapy but without demonstrable benefit.

The mother stated that the patient had always been mildly dyspneic and this was exaggerated on even slight exercise. He would often awake in the

morning covered with sweat and would be too weak to sit up. During this entire time there had been a gradual increase in the size of his abdomen. His development had been normal in every respect except as previously indicated. He had had few respiratory infections and no other illnesses.

The boy had been under the care of several physicians before being seen here. At 8 months of age a biopsy was obtained of the liver. Unfortunately, the exact glycogen content of the tissue was not obtained. However, Best's carmine stain revealed a marked increase in the glycogen content of nearly all cells. There were no cirrhotic changes present. The fat content, by histologic examination, was not considered abnormal.*

At one year of age he was admitted for studies in another hospital. At that time his weight was 23 pounds, his height was 29½ inches, and the liver was markedly enlarged. A glucose tolerance test using 25 Gm. of glucose by mouth was carried out with the results shown in Table I:

TABLE I

	BLOOD SUGAR
Fasting	48 mg. per cent
1½ hour	97 mg. per cent
1¾ hours	136 mg. per cent
2 hours	100 mg. per cent
2½ hours	63 mg. per cent
3 hours	44 mg. per cent

There was no appreciable response of the blood sugar to an injection of epinephrine at 15-, 30-, or 45-minute intervals. Following ingestion of 16 Gm. of galactose none was found in the urine within a three-hour period. After being on 32 mg. of desiccated thyroid for one month a repetition of the glucose tolerance test was carried out with results similar to the original test.†

The family history was essentially none contributory to the present illness. Both parents were living and well and one younger sibling was apparently normal. There was no evidence of a similar disease in either side of the family. Before becoming pregnant with the patient the mother had received thyroid and "injections of pituitary" for amenorrhea for a brief period.

Physical examination at this hospital on Jan. 12, 1948, revealed a child who appeared undernourished but not acutely ill. His height was 32 inches and his weight was 26.5 pounds. The most striking feature on general inspection was the great enlargement of the abdomen in an otherwise very slender body habitus. His respirations were somewhat labored, and this was increased by even very mild exertion. His gait and posture were normal for his age. His mentality seemed normal and he was cooperative and of a pleasant disposition. There was a generalized shotty lymphadenopathy involving the cervical, postauricular, and inguinal nodes. The veins were unusually prominent over the protuberant abdomen. The liver displaced the diaphragm about three finger-widths upward on the right as compared to the left. The border of the liver could be palpated from the left upper quadrant extending downward into the right iliac fossa. The edge was sharp, firm, smooth, and none tender. It was so large that palpation for other organs or masses in the abdominal cavity was

*We are indebted to Dr. E. Berkley Neal, of Roanoke, Va., for the report of the biopsied material.

†The results of these tests were kindly furnished us by Dr. P. J. Howard of the Pediatric Department of Henry Ford Hospital, Detroit.

unreliable. No fluid was demonstrable. The only other remarkable finding was that the anterior fontanelle was patent and admitted one finger. (He had received adequate vitamin D intake since very early infancy.)

Routine laboratory studies were as follows: hemoglobin 11.5 Gm., 3.6 million red blood cells, 13,200 white blood cells, a normal differential blood count, urinalysis was negative except for a strongly positive acetone test after a six-hour fasting period. The test for diacetic acid was negative on this same specimen.

The morning after admission the patient had fasted for eight hours. He was very irritable, sweating profusely, and appeared to the mother to be going into one of his mild convulsive seizures. At this time the patient was given 1.70 Gm. of gelatin per kilogram of body weight and within fifteen minutes he was quiet, comfortable, stopped sweating, and became cooperative. After ingestion of the gelatin he was fasted for four hours and the amino acid content of the blood was determined at frequent intervals during this time.⁸ Within one-half hour there was a rise of more than 2 mg. per cent and this rise was sustained over the four-hour period. We interpret this test as showing an adequate absorption of protein from the gastrointestinal tract.

Because of the apparent relief in symptoms due to ingestion of protein, the following morning the same procedure was followed except that blood sugar determinations were made. Table II shows the results obtained.

TABLE II

TIME	BLOOD SUGAR (CAPILLARY)
Fasting	45.0 mg. per cent
½ hour	67.5 mg. per cent
2 hours	97.5 mg. per cent
4 hours	75.0 mg. per cent

Blood sugar determinations were then made on two subsequent days using two separate diets throughout each day. Both diets contained approximately 1,400 calories. On the first day, 60 per cent of the calories were in the form of carbohydrate and 15 per cent as protein. On the second day 40 per cent of the caloric intake was protein and about 30 per cent as carbohydrate. Fig. 1 shows the response of the patient's blood sugar to each diet.

We took advantage of the patient's presence to do certain other metabolic studies. These revealed a normal rate and level of absorption of an oily preparation of vitamin D taken orally; normal blood levels of calcium, phosphorus, phosphatase, and pyruvic and lactic acids; stool fat was 2 per cent by dry weight; total urine organic acid excretion in twenty-four hours was equivalent to 160 c.c. of 0.1 N hydrochloric acid (a value well above average ranges); acid-base studies on venous blood revealed the following values:

HCO ₃	19.6 meq. per liter
Chloride	98.0 meq. per liter
Protein	18.4 meq. per liter
Total base	152.5 meq. per liter
pH	7.31

Roentgenograms of the chest were negative for many abnormalities of the heart, lungs, or thoracic cage. There was no marked retardation of skeletal maturation, as judged by the appearance of carpal centers.

Because a low carbohydrate and high protein diet resulted in less fluctuation of the blood sugar throughout the day and in less of a drop of the blood sugar after fasting for six to eight hours, the patient was discharged from the hospital on that type of a diet. This was calculated to average 1,400 calories daily and contained protein 140 Gm., fat 50 Gm. and carbohydrate 80 to 100 Gm.

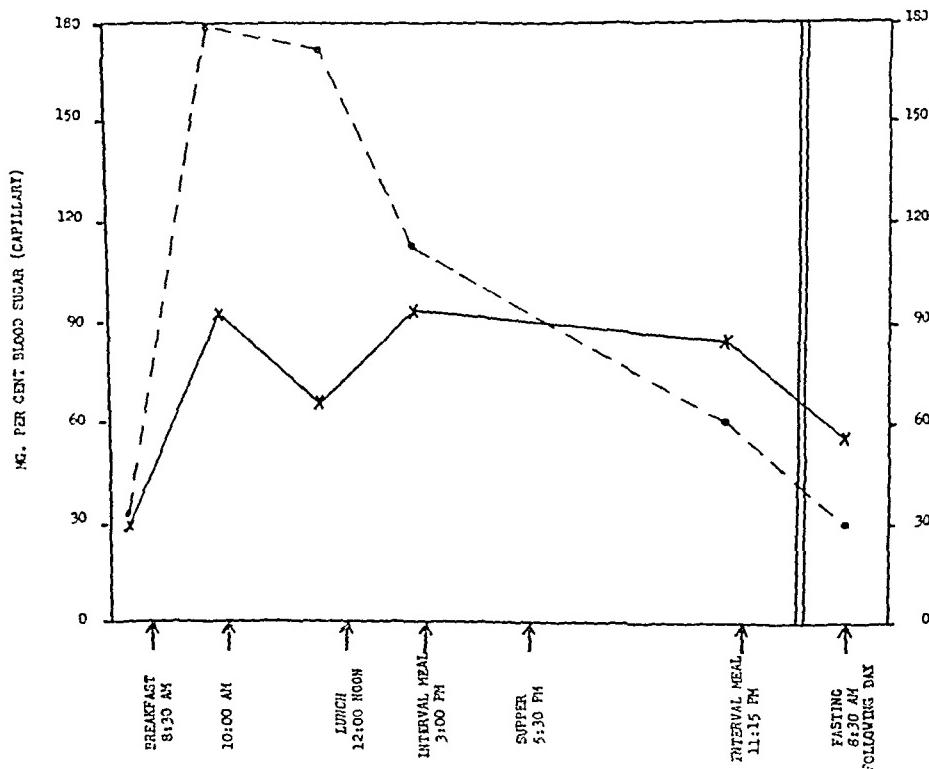


Fig. 1.—Response of the blood sugar level of a patient with glycogen storage disease to changes in diet. The broken line represents the levels obtained while on a high carbohydrate diet. The solid line represents the blood sugar levels obtained while on a high protein-low carbohydrate intake. The determinations were all made before the ingestion of food as indicated and extended over a twenty-four hour period.

The boy returned to this clinic for observation after a year on this regimen. His height was 34½ inches (a gain of 2¾ inches in one year which is slightly less than normal for his age); his weight was 31 pounds (a satisfactory gain although the patient was still below normal weight for age). The abdomen was still very large, but the liver size was estimated to have remained stationary. The anterior fontanelle was closed. He was very cooperative, active, and mentally alert. There appeared to be less dyspnea with exertion than a year previously.

He had religiously adhered to the prescribed diet and his mother stated that at no time did she have difficulty in getting him to eat it. Both of his

parents were enthusiastic over his response to this treatment. He had had no convulsions during the entire year. This was in marked contrast to his previous history when the longest interval between convulsions was two or three months. He no longer had early morning sweats or weakness. He could now be dressed and eat his breakfast with the family rather than being fed immediately upon awakening in the morning. He could fast for as long as fifteen hours without symptoms. It was not necessary to give a late night interval feeding, although he continued to get this occasionally. He played more actively than formerly without undue tiredness or exhaustion. Except for a mild upper respiratory infection, he had been quite well.

Laboratory studies showed a hemoglobin value of 11.5 Gm. and a white blood count of 12,000. An early morning urine was entirely negative except for a strongly positive acetone test. The acetone disappeared during the day but was present again in another fasting specimen. Capillary blood sugar determinations were as follows: before breakfast 28 mg. per cent on one occasion and 46 mg. per cent on another, before lunch 81 mg. per cent, and before supper 68 mg. per cent. During these determinations his eating habits and diet were planned to correspond exactly to those in his home. Blood levels of calcium, phosphorus, phosphatase, electrolytes, and total protein were similar to those obtained when first observed.

The child has continued to progress as described up to the present time (aged 3½ years), and he has not experienced further convulsions over a period of nearly eighteen months. He has only three meals a day.

DISCUSSION

All attempts at the treatment of glycogen storage disease have been very disappointing. A very obvious reason for this was the absence of a sound knowledge of the pathogenesis of the disease. It is now generally recognized that the hepatic form of this condition is caused by an abnormality of the enzyme system which is essential for the mobilization of glycogen stored in the liver. It would appear from experimental evidence that the glycogen itself is not different from that found in the livers of normal subjects.³⁻⁵

A logical conclusion from these observations would be to supply the missing or abnormal enzymes necessary to liberate the glycogen depots. Such an approach was attempted by Bridge and Holt⁴ who administered pancreatic extracts both orally and by injection to patients with von Gierke's disease. The results of this method of therapy were unsuccessful. No similar attempts have been made by others.

The various methods of treatment have been reviewed at some length by van Creveld.¹ Many endocrine preparations have been used including pituitary extracts,¹ thyroid,^{1, 2} various fractions of the adrenal cortex,^{1, 4} and epinephrine. None of these have resulted in any appreciable change in the disease when used alone or in various combinations. Other agents which have been tried include whole liver, liver extracts, choline, cholic acid, lecithin, and x-radiation. None of these have been of value in well-substantiated cases of glycogen storage disease.¹⁻⁴ Furthermore, there seems to be no logical rationale behind their use.

Bile salts were used by Matheson¹⁷ in the treatment of a case. He reported "disappearance of ketonuria and decrease in girth of the abdomen" as the result of such therapy. However, even slightly prolonged periods of fasting caused reappearance of acetone in the urine, and there was no reduction in the palpable size of the liver after several months. Finally, the response of blood glucose to injections of epinephrine remained lower than normal in spite of treatment. This patient had never manifested any symptoms due to hypoglycemia. It is difficult to see how bile salts would influence the enzyme system in the liver.

Since it seems improbable to attack the fundamental defect in this condition at the present time, we are left with only symptomatic therapy. Aside from the very marked enlargement of the liver and the physical embarrassment caused by it, a major symptom results from the associated hypoglycemia. This was certainly true in our patient and in many others reported in the literature. Two factors apparently may lead to the production of symptoms in cases of hypoglycemia regardless of their cause. First, but not necessarily of primary importance, is the rapidity of the fall in blood sugar, and second, the relative carbohydrate starvation of tissues regardless of the blood level. It has been pointed out that the latter explanation may account for hypoglycemic reactions when blood sugar is at a normal level, or the absence of such reactions when this level is abnormally low.⁹ Although the variations in the glucose content of the blood are important, the activity of the brain in controlling its own consumption of glucose appears to be of greater significance^{9, 10}. It may be postulated that a slow drop in the blood sugar for brief periods finds the brain and other tissues in a condition set to maintain themselves until the supply again becomes available.

Conn¹¹ suggested the use of a high protein diet in the treatment of hyperinsulinism. He was able to prove that such a measure resulted in a better sustained blood sugar level than any other diet, and that it resulted in more satisfactory symptomatic treatment than frequent feedings of carbohydrate. Such a diet, due to the relatively slow gluconeogenesis from protein, will supply a more constant source of glucose for the body. Bridge and Holt⁴ suggested that a "protein meal" before bedtime for one of their patients with von Gierke's disease led to considerable improvement of the hypoglycemia. Later Bridge² mentioned a high protein intake as a part of therapy but continued to rely upon frequent feedings as a major portion of the therapeutic program.

It is possible that reducing the carbohydrate intake in a patient with glycogen storage disease will reduce the available sugar that can be converted and stored as liver glycogen. It must be admitted that such reasoning is purely hypothetical. If such treatment could be started very early in life, would the hepatomegaly be less pronounced?

The only treatment given to our patient was that of placing him upon a high protein and low carbohydrate diet. This resulted in very dramatic improvement of his symptoms which has continued up to the present time. Hypoglycemia and acetonuria are still in evidence and the degree of hepatomegaly has remained the same as before the special diet was begun. We are, therefore,

forced to conclude that the beneficial effect is due to the less rapid fluctuation and drop of the blood sugar levels when on a high protein-low carbohydrate intake. Laboratory evidence lends support to this contention.

SUMMARY

A typical case of the hepatic type of von Gierke's disease in a 2-year-old boy is reported. Symptoms associated with hypoglycemia were a prominent part of the condition. He was put on a high protein and low carbohydrate diet with very dramatic relief of these symptoms. Laboratory evidence supports the clinical impression that improvement was due to the more sustained blood sugar levels and less rapid fall to hypoglycemic values when placed on such a diet. It is probable that the fundamental disease process was little altered by such therapy.

We wish to express our appreciation to Miss Jean Fulkerson, head dietitian for the pediatric services, who aided us very greatly in calculating all of the diets and making valuable suggestions as to various foods to use in them.

REFERENCES

1. van Creveld, S.: Glycogen Disease, *Medicine* 18: 1, 1939.
2. Bridge, E. M.: Glycogen Storage Disease, in *Brennemann's Practice of Pediatrics*, vol. 3, chap. 24-A, Hagerstown, Md., 1948, W. F. Prior Co., Inc.
3. Mason, H. H., and Anderson, D. H.: Progress in Pediatrics: Glycogen Disease, *Am. J. Dis. Child.* 61: 795, 1941.
4. Bridge, E. M., and Holt, L. E., Jr.: Observations of the Pathologic Physiology of Two Cases of the Hepatic Form of the Disease, *J. PEDIAT.* 27: 299, 1945.
5. Crawford, T.: Glycogen Disease, *Quart. J. Med.* 39: 285, 1946.
6. Thomas, E. M.: Total and Fractional Blood Lipid Levels in Diseases of Childhood, *Am. J. Dis. Child.* 74: 563, 1947.
7. Wagner, R.: Glycogen Content of Isolated White Blood Cells in Glycogen Storage Disease, *Am. J. Dis. Child.* 73: 559, 1947.
8. West, C. D., Wilson, J. L., and Eyles, R.: Blood Amino Nitrogen Levels, Changes in Blood Amino Nitrogen Levels Following Ingestion of Proteins and of a Protein Hydrolysate in Infants With Normal and With Deficient Pancreatic Function, *Am. J. Dis. Child.* 72: 251, 1946.
9. Fabrykant, M., and Bruger, M.: Dynamics of the Hypoglycemic Reaction, *Am. J. M. Sc.* 216: 84, 1948.
10. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Interpretations, vol. I, Baltimore, 1946, Williams and Wilkins Co., pp. 229-329.
11. Conn, J. W.: The Spontaneous Hypoglycemias, Importance of Etiology in Determining Treatment, *J. A. M. A.* 115: 1669, 1940.
12. Abramson, H., and Kurtz, L. D.: Familial Glycogen Disease, Report of Four Fatal Cases of the Disease in Siblings of One Family, *Am. J. Dis. Child.* 72: 510, 1946.
13. Humphreys, E. M., and Kato, K.: Glycogen Storage Disease, Thesaurismosis Glyco-genica (von Gierke), *Am. J. Path.* 10: 589, 1934.
14. Kramer, B., Grayzel, H. G., and Solomon, C. I.: Chronic Hypoglycemia in Childhood, *J. PEDIAT.* 5: 299, 1934.
15. Mellinkoff, S., Roth, B., and MacLaggan, J.: Galactosemia With Hepatic Damage, *J. PEDIAT.* 27: 338, 1945.
16. Mason, H. H., and Turner, M. E.: Chronic Galactemia. Report of a Case With Studies on Carbohydrates, *Am. J. Dis. Child.* 50: 359, 1935.
17. Matheson, W. J.: Glycogen Disease of the Liver, With Report of a Case, *J. PEDIAT.* 34: 537, 1949.

THE EFFECT OF PREOPERATIVE ROENTGEN-RAY THERAPY ON ARTERIAL HYPERTENSION IN EMBRYOMA (KIDNEY)

J. EDMUND BRADLEY, M.D., AND MILES E. DRAKE, PH.D., M.D.
BALTIMORE, MD.

ROENTGEN-RAY irradiation of the adrenals¹ to reduce arterial hypertension has been reported and paradoxically the kidneys of dogs have been irradiated to produce experimental arterial hypertension.² The effect of preoperative roentgen-ray irradiation on hypertension in eleven cases of renal embryoma (Wilms' tumor) was reported by Daniel.³ Briefly, the results obtained by this author were that in a total of five patients who had extreme arterial hypertension (125 mm. Hg or more), three had a marked reduction of the blood pressure within three weeks, one had no apparent change in blood pressure, and the remaining patient had a massive hemorrhage into the tumor with resultant shock and anemia, before the blood pressure could be determined. Six patients with normal or only moderate elevation of blood pressure (110 to 125 mm. Hg) demonstrated no alteration in blood pressure readings.

In the original description⁴ of the association of hypertension with Wilms' tumor, we reported five cases in which hypertension was present. There was only one case in this series in which preoperative irradiation had been used, and in this case widespread metastases was exhibited to the skull and orbit, as well as to the liver; there was no effect upon the extremely elevated blood pressure. Since our original report there have been twelve cases of Wilms' tumor admitted to the University Hospital. Ten of these patients had hypertension. These ten patients were given preoperative roentgen-ray irradiation. As seen in Table I, blood pressure determinations were not made on patient No. 6, and in patient No. 5 there was no clinical evidence of hypertension. Four patients given preoperative irradiation had a marked fall in blood pressure five to eight days after the beginning of treatment. Three of these four patients had a detectable reduction in size of the tumor, but this was preceded in all cases by the change in blood pressure. Two of the patients (Nos. 7 and 9) in this treated group are still alive after five and one-half and eight years, respectively. The blood pressure of both are well within normal limits at the present time. Six patients given preoperative irradiation did not respond with any lowering of blood pressure or in the size of the tumor five to eight days after beginning treatment. One patient (No. 10) had no reduction in tumor size even though there was reduction in blood pressure. One patient (No. 8) had a normal blood pressure (Fig. 1) following preoperative irradiation, which persisted following nephrectomy and remained within normal range until six months later, when with the development of pulmonary metastases hypertension occurred. Irradiation to this area resulted in a return of the blood pressure to normal limits. There was no evidence clinically or by roentgenologic examination of recurrence of the tumor at the original site. However, upon her return four months later

From the Department of Pediatrics, University of Maryland School of Medicine, and University Hospital.

TABLE I

NO.	PATIENT	AGE	SEX	BLOOD PRESSURE			TOTAL UNITS OF X-RAY THERAPY	TUMOR RESPONSE TO X-RAY	OPERATION	BLOOD PRESSURE		COMMENT	RESULT
				BLOOD PRESSURE ON BEGINNING OF ADMISSION	BLOOD PRESSURE END OF X-RAY THERAPY	TOTAL UNITS OF X-RAY THERAPY				POST-OPERA-TIVE	BLOOD PRESSURE DISCHARGE		
1.	W.B.	18 mo.	M.	170/132	156/118	1530	172/118	No apparent change	Nephrectomy	—	—	Enthus on table	Died
2.	W.S.	5 yr.	M.	156/110	154/98	2214	136/80	No apparent change	Laparotomy	142/86	126/90	Inoperable tumor	Died
3.	J.B.	5 yr.	F.	140/110	120/90	2250	90/60	Mass reduced in size	Nephrectomy	106/76	102/78	2 mo. later widespread metastasis	Died
4.	M.L.	19 mo.	F.	110/98	114/92	2872	118/88	No apparent change	Laparotomy	114/90	122/90	Death one month later	Died
5.	M.E.	4 yr.	F.	100/70	—	—	—	—	Nephrectomy	102/68	98/70	Postoperative irradiation given	Still alive 8 mo.
6.	I.S.	3½ yr.	F.	?	?	2666	?	No apparent change	Laparotomy	?	?	Cachexia and death one month later	Died
7.	C.M.	17 mo.	M.	140/92	140/90	1936	110/66	Mass reduced in size	Nephrectomy	92/58	90/60	3 years later B.P. 92/58	Living after 5½ yr.
8.	E.B.	8 yr.	F.	168/124	150/110	2536	120/82	Mass reduced in size	Nephrectomy	120/80	110/74	Metastasis to liver and lungs	Died
9.	G.L.	2½ yr.	F.	170/110	144/104	1212	114/68	Mass reduced in size	Nephrectomy	104/60	100/60	Blood pressure normal	B.P. normal 8 yr. later
10.	N.B.	3½ yr.	F.	140/100	144/100	1261	104/78	No apparent change	Laparotomy	100/70	100/70	B.P. 6 weeks postoperative 140/110	Died
11.	M.H.	6 yr.	M.	160/122	158/118	1224	152/120	No apparent change	Laparotomy	156/116	—	Widespread metastasis to skull, liver, lungs, orbit	Died
12.	M.A.	1 yr.	F.	130/80	126/86	1670	130/76	No apparent change	Nephrectomy	130/84	126/94	Readmitted 5 mo. later B.P. 130/100. Pulmonary metastasis	Died

there was a large mass filling the entire right abdomen and there had been an increase in the pulmonary metastases. During this admission the patient suddenly one evening became speechless and developed temporary blindness and loss of hearing; shortly thereafter the patient had a generalized convulsive seizure. The blood pressure reading at this time was 220/160 mm. Hg. The convulsions were finally controlled after one hour with sodium luminal and magnesium sulfate. Death of this patient occurred eleven and one-half months following the initial admission. A post-mortem examination showed widespread pulmonary and hepatic metastases, but no evidence of tumor recurrence at the original site and with no involvement of the right kidney.

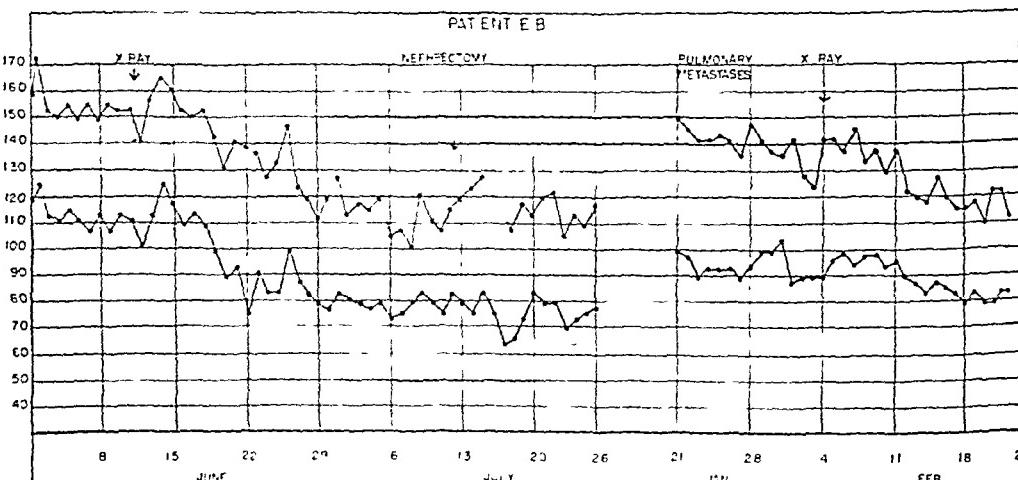


Fig. 1.

DISCUSSION

The cause of the hypertension seen in Wilms' tumor remains unknown. At the time of the original report of the occurrence of arterial hypertension with Wilms' tumor it seemed significant that⁵ we were reporting a unilateral renal lesion with clinically manifest hypertension which seemed to confirm Goldblatt's experimental observations. Added significance seemed to be attached to our observation when Page⁶ produced hypertension in the dog by wrapping one kidney in cellophane. The resultant appearance of the dog's kidney was not at all unlike the gross appearance of Wilms' tumor with the striking separation of encapsulated tumor from apparently normal renal tissue. However, as more and more cases of unilateral renal lesions with hypertension were reported, it became increasingly apparent that the experimental work of Goldblatt, Page, and others had but limited clinical application. So the advocates of hypertension of renal or a focal vasoconstrictor origin continue to be pressed by those who adhere to a neurogenic and a general vasospastic origin. The hypertension seen in Wilms' tumor does not offer any particular solution to the problem but presents rather new problems. While the preponderant majority of patients with renal

embryoma have an associated hypertension, some do not, as seen in patient No. 5. The variability of the hypertension is also of interest. Some have a very marked hypertension, others of only a moderate degree. Apparently the severity of the hypertension does not provide any prognostic index as in patient No. 9 where a 2½-year-old white girl had an admitting blood pressure reading of 170/110 and yet this patient is alive eight years later. Daniel in his report stated that irradiation probably reduces the hypertension by reducing the size of the tumor mass and thereby lessening the amount of ischemia. In our series, patient No. 10 had a reduction of hypertension but there was no palpable reduction in the size of the tumor. The concept of renal ischemia seemed quite tenable when at post-mortem examination of patient No. 2 in this series there was probably interference with circulation of the uninolved kidney due to invasion of the inferior vena cava by tumor tissue. This concept also seemed particularly applicable in those cases where with removal of the tumor or with reduction in tumor size by irradiation the blood pressure would return to normal limits. However, the renal ischemia theory does not seem applicable to those cases where metastatic lesions in the lungs and in the liver were associated with a return of hypertension, and further, when irradiation was given over the metastatic areas the blood pressure returned to lower levels.

Originally, we⁴ speculated as to whether the tumor tissue itself could be responsible for the hypertension. If this were true then it would seem logical that this could be the explanation of the above cited case. One could also reasonably expect to find a pressor substance present in these tumors. Repeated attempts on our part have failed to demonstrate the presence of any pressor substance. It would also be expected that hypertension would be present in all cases of Wilms' tumor. Such has not been our experience or the experience of other investigators. We, in our entire series, found it absent in one patient out of a total of sixteen patients for an incidence rate of 93.8 per cent; Daniel³ found hypertension present in 77.9 per cent, and Silver⁷ in 87.5 per cent. In an attempt to determine whether there was any alteration in the microscopic appearance of tumor tissue in those individuals who had marked hypertension and those who had less marked hypertension or normal pressure, we have carefully examined all tumor sections and we have not been able to detect any cellular pattern that conforms to the various clinical blood pressure manifestations.

It is interesting that irradiation in a number of our patients resulted in a substantial fall in blood pressure particularly when renal irradiation has been used to produce experimental nephritis and hypertension. The failure of a number of patients to respond with any reduction in tumor size as a result of irradiation is contrary to statements made by many authors that these tumors are extremely sensitive to roentgen-ray therapy. There does not seem to us to be any advantage in the use of preoperative irradiation except in those cases where the tumor size is such that it is surgically unmanageable and must be reduced in size.

The occurrence of hypertension with unilateral renal lesions does suggest a causative renal factor. However, the failure of hypertension to occur in all

eases of renal embryoma, and even more striking the apparent occurrence of hypertension due to metastatic lesions in organs other than the kidney, is suggestive of other factors than renal ischemia being responsible for the hypertension in these cases.

SUMMARY

The effect of the use of preoperative roentgen-ray therapy on ten patients with arterial hypertension which was found in association with embryoma of the kidney is reported.

REFERENCES

1. Boswell, F. P.: Results of Roentgen Therapy in Essential Hypertension, *South. M. J.* 31: 1001-1003, 1938.
2. Hartman, I. W., Ballenger, A., and Daub, H. P.: Experimental Nephritis Produced by Irradiation, *Am. J. M. Sc.* 172: 187-500, 1926.
3. Daniel, W. E.: The Hypertensive Factor in Wilms' Tumor, *South. M. J.* 32: 1014-1016, 1939.
4. Bradley, J. L., and Pineoffs, M. C.: The Association of Adeno-myo-sarcoma of the Kidney (Wilms' Tumor) With Arterial Hypertension, *Ann. Int. Med.* 11: 1613-1627, 1938.
5. Goldblatt, H.: Studies on Experimental Hypertension. B. The Pathogenesis of Experimental Hypertension Due to Renal Ischemia, *Ann. Int. Med.* 11: 69-103, 1937.
6. Page, I. H.: Production of Persistent Arterial Hypertension by Cellophane Perinephritis, *J. A. M. A.* 113: 2846-2849, 1939.
7. Silver, H. K.: Wilms' Tumor (Embryoma of the Kidney), *J. PEDIAT.* 31: 643-650, 1947.

INCIDENCE OF MYCOTIC INFECTIONS IN CHILDREN WITH ACUTE RESPIRATORY DISEASE

FRANCES C. WHITCOMB, M.S., ALBERT MILZER, PH.D., M.D., AND
RALPH H. KUNSTADTER, M.D.
CHICAGO, ILL.

WITHIN the past decade the concept that pulmonary calcifications are almost invariably of tuberculous origin has been challenged. In 1942 Aronson, Saylor, and Parr,¹ on the basis of tuberculin and coccidioidin tests, demonstrated that coccidiomycosis is probably the cause of pulmonary calcification in negative tuberculin reactors among the Indian children in the Southwest. Long and Stearns² found that inductees from the East Central part of the United States had a greater incidence of pulmonary calcifications than inductees from other parts of the country. C. E. Smith³ suggested that histoplasmosis might be the cause of pulmonary calcification in negative tuberculin reactors in the East Central and Middle Western parts of the United States. Christie and Petersen⁴ and Palmer⁵ showed that a correlation exists between histoplasmin sensitivity and pulmonary calcification in individuals with negative tuberculin skin tests. Bunnell and Furcolow⁶ have pointed out that whenever extensive search for histoplasmosis is made there is a marked increase in the number of cases reported. They reported ten proved cases of histoplasmosis; two of the ten patients recovered.

The purpose of the present study was to conduct skin tests and cultural and serologic studies for pathogenic, systemic fungi in children with acute respiratory disease, including pneumonia. Special note was made of children with a history of allergy. Cross reactions between histoplasmin and other fungus antigens and the effect of skin testing on patients under treatment with antibiotics were also noted. The studies were made on patients admitted to the Sarah Morris Hospital for children. Emphasis was placed on children whose roentgenograms showed early pulmonary infiltrations as well as nodular, focal, or fibrotic lesions. The children ranged in age from 3 weeks to 14 years. A total of 211 children were studied. Sixty-three had clinical and x-ray findings of pneumonia, while seventy-two had acute upper respiratory infections. The remaining seventy-six children had no evidence of infectious disease, and these served as controls. All of the children were skin tested and cultured for pathogenic bacteria and fungi. Complement fixation tests were done only on the children with x-ray evidence of pneumonia and positive skin tests.

As a result of these studies three proved and two presumptive cases of fungus infections were demonstrated: (1) a case of benign histoplasmosis with symptoms of atypical pneumonia to be described fully elsewhere¹²; (2) a fatal

From the Department of Bacteriology and Virology, Medical Research Institute, and the Sarah Morris Hospital for Children, Michael Reese Hospital, Chicago.

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infection due to an unidentified fungus producing granulomatous lesions of the lung, liver, and kidney; (3) *Candida albicans* infection of the lung associated with malnutrition; and (4) two children whose x-ray findings and clinical symptoms were comparable with a cases of geotrichosis previously reported.⁷

MATERIAL AND METHODS

The children were routinely skin tested with histoplasmin,^{*} blastomycin,^{*} eococcidioidin,[†] torulin,[‡] and tuberculin (PPD).[§] These were prepared from the mycelial phase of the following fungi, respectively: *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Coccidioides immitis*. They were used in dilutions of 1:1,000. PPD was used in dilution of 0.0001 mg.

The antigens were injected intracutaneously in 0.1 c.c. amounts into the volar surface of the forearm. A separate set of syringes and needles was used for each antigen. The skin tests were read at the end of forty-eight hours, at which time both induration and erythema were noted and measured. Reactions of 5 mm. or more of induration measured forty-eight hours after injection were considered positive. All others were interpreted as negative. The injections were done by the same person, and the skin tests were read and measured independently by two of us.

Chest x-rays were made routinely of children with acute respiratory disease on standard x-ray films (8 x 10 inches or larger). The films were read by the roentgenologist of Michael Reese Hospital without knowledge of results of the skin tests.

Each child was routinely cultured with a nasopharyngeal swab on media suitable for growth of bacterial as well as fungus pathogens. Repeated gastric lavage, blood, stool, and, in some instances, bronchial secretions in selected cases whose x-ray showed pneumonic infiltrates were cultured. All specimens were collected in sterile containers and planted immediately. A thorough search was made for the tubercle bacillus using Petragnani and egg yolk media, guinea pig and mouse inoculations.⁸ Fungus cultures were planted in duplicate on plates containing cystine brain-heart infusion agar with 20 and 40 units of penicillin and streptomycin per cubic centimeters respectively. One plate was incubated at 37° and the other at 25° C. Littman's media,⁹ potato dextrose, and Sabouraud's media were also inoculated with each specimen and incubated at 25° C. Cultures for actinomycetes were made on beef infusion agar using the spray dish technique.¹⁰

Serum was drawn from patients with positive fungus skin reactions and x-ray findings of pneumonic infiltrates for fungus complement fixation tests. The technique of Tenenberg and Howell was used.¹¹ Complement fixation tests were done on approximately 75 per cent of positive fungus skin test reactors with pneumonic infiltrates. Histoplasmin and blastomycin antigens for the

*Furnished through the courtesy of Dr. Arden Howell of the United States Public Health Service.

†Furnished through the courtesy of Dr. Charles H. Smith of Stanford University.

‡Furnished through the courtesy of Eli Lilly & Co.

§Furnished through the courtesy of the Tuberculin Institute of Chicago and Cook County.

complement fixation tests were furnished by Eli Lilly and Co. Doubtful and positive results were repeated using II15 histoplasmin and B7 blastomycin antigens.

RESULTS

The results of the fungus and tuberculin skin tests in the three groups of children studied are summarized in Table I. As shown in Table I, no significant difference was found between the three groups of children studied. All positive skin tests for the fungus antigens were obtained during the acute stage in children with respiratory disease. Approximately 25 per cent of the negative reactors were given repeat skin tests after two weeks with negative results. An additional 15 per cent were retested six weeks to three months after the initial test, again with negative results.

TABLE I. SUMMARY OF RESULTS OBTAINED WITH SKIN TEST ANTIGENS IN TWO HUNDRED ELEVEN CHILDREN WITH VARIOUS CLINICAL FINDINGS

SKIN TEST ANTIGEN REACTION	NO. WITH EVIDENCE OF PNEUMONIA	NO. WITH UPPER RESPIRATORY INFECTIONS	CONTROLS (NO EVIDENCE OF INFECTIOUS DISEASE)
Histoplasmin-negative, tuberculin-positive	7	13	13
Histoplasmin-positive, tuberculin-positive	1*	3	4
Histoplasmin-positive, tuberculin-negative	3	3	3
Blastomycin-positive, tuberculin-negative	1	0	0
Blastomycin-positive, tuberculin-positive	1	0	1
Torulin-positive only	0	1	1
Geotrichum-positive only	1	0	0
Geotrichum-positive, coccidioidin-positive	1	0	0
Negative reactors	48†	52	54
Total no. tested	63	72	76

**H. capsulatum* was isolated and a positive histoplasmin complement fixation test was also demonstrated (Case 1).

†Includes two patients who died of miliary tuberculosis.

Three positive cultures of significant pathogenic fungi were obtained. One strain of *H. capsulatum* was isolated from the blood during the acute stage from a child (Case 1) with "atypical pneumonia." This patient also had a positive complement fixation and skin test for histoplasmosis. This case is discussed in greater detail below. An unidentified fungus was isolated from a fatal case with granulomatous lesions of the lung, liver, and kidney (Case 2). Finally, *C. albicans* was isolated repeatedly from an infant with pneumonia and malnutrition. Although about 5 per cent of the nasopharyngeal cultures of the three groups of children were positive for *C. albicans*, we believe that the isolation of *C. albicans* in Case 3 is significant because this fungus was isolated repeatedly in predominant numbers from gastric lavage, bronchial secretions, and stool cultures of this child. Furthermore, he responded to therapy with large doses of iodides. Negative results were obtained in cultures for other pathogenic fungi. The usual pathogenic bacteria were recovered in throat cultures of the group of children with acute upper respiratory tract infections. No significant pathogenic bacteria were isolated in most instances from the pneumonia group. Negative results were obtained in complement fixation tests with fungus antigens except for the positive histoplasmosis in Case 1. The following is a

brief abstract of the clinical records of the three proved and two presumptive cases of fungus infections encountered during the present study.

CASE 1.—The patient, J. G., a Negro boy aged 12 years, had numerous admissions into Sarah Morris Hospital with a diagnosis of rheumatic heart disease. He was readmitted September 4 after a vacation at a summer camp where he developed an acute respiratory infection. At this time he was positive to histoplasmin (7 mm. induration) and tuberculin (13 mm. induration). The tests for other fungus antigens were negative. Complement fixation tests were positive for histoplasmin only on Dec. 1, 1948 (4 plus), December 20 (3 plus), and April 2, 1949 (2 plus). On November 17 he was readmitted with a diagnosis of atypical pneumonia. He was now positive to histoplasmin (20 mm. induration) and tuberculin (10 mm. induration). Other fungus antigens remained negative. The roentgenogram revealed a large patch of parenchymal infiltration in the left midlobe. *H. capsulatum* was isolated from a blood culture drawn November 17. Cultures of bronchial secretions, gastric washings, and stools were negative for *H. capsulatum* and the tubercle bacillus. Guinea pig and dba mice inoculations for tubercle bacillus were also negative. The bronchial secretions and gastric lavages were inoculated into two groups of six white mice each, which were sacrificed after varying intervals. One mouse inoculated with bronchial secretions and sacrificed after six weeks revealed a few tubercle-like lesions in the liver and spleen from which *H. capsulatum* was isolated. This case is reported fully elsewhere.¹²

CASE 2.—The patient, N. C.,^{*} a 3-year-old child, had been admitted into the hospital at various times with anemia, enlarged lymph nodes, splenomegaly, and skin lesions. He was readmitted in September, 1946. At this time the Mantoux test formerly negative became 3 plus. His abdomen was distended. A paracentesis was done, and the fluid obtained was examined and cultured for the tubercle bacillus with negative results. He received x-ray therapy and after a stormy course was discharged with the diagnosis of tuberculous peritonitis. He was admitted once more in November, 1946. The clinical findings and x-ray were compatible with osteomyelitis. The Mantoux and histoplasmin skin tests were negative at this time.

His final admission was on May, 1947. He had large white patches in the mouth, and the liver was markedly distended. An exploratory operation was done and a large abscess filled with caseous material was seen in the liver. No organisms were seen on direct smear. The pus was cultured and an unidentified fungus was isolated which grew in cream to gray-colored colonies after incubation at room temperature or 37° C. for five days.

The patient went downhill rapidly and died. At autopsy the lungs, liver, and kidney showed numerous granulomatous lesions. The same fungus was isolated. Microscopic sections showed gram-positive mycelia in the lungs. The organism isolated is not one of the known pathogens and so far has not been identified. Mice inoculated with the organism developed abscesses in the skin, peritoneum, and liver. The patient's brother died of the same type of disease two years previous with similar findings at autopsy. Sections of the tissues of the latter showed no mycelia.

CASE 3.—L. W., a 7-month-old Negro male infant, was transferred to this hospital with pulmonary pathology involving the right apex suspected of being either pneumonia or tuberculosis. His emotional and somatic development were retarded. *C. albicans* in predominating numbers was isolated repeatedly from

*This case is reported with the permission of Dr. Philip Rosenblum, attending physician of Sarah Morris Hospital.

gastric lavage, bronchial secretions, and stool cultures. Skin tests with the various fungus antigens and tuberculin were negative except for Candida. It was noted that he had repeated asthmatic attacks. He was found to be sensitive to both human and cow's milk. A diagnosis of food allergy with secondary pulmonary infection due to *C. albicans* was made. The patient began to improve gradually with dietary regulation and large doses of iodides.

CASE 4.—The patient, R. Y., aged 6 years, had a fever of six months' duration. He was a thin, white male child who appeared chronically ill. The initial signs of the onset of illness were a sore throat and coryza. He developed a productive cough. Three weeks after onset of fever the x-ray showed lung pathology. Streptomycin therapy was instituted with no effect. The sputum was white and mucoid but never blood-tinged. The patient lived with his family near a stone quarry and had never left Kankakee, Ill. His skin test remained negative to all fungus antigens and repeated cultures were negative for pathogenic fungi. Because of the similarity of this case, both clinically and in x-ray findings, to a case of geotrichosis reported by one of us,⁷ it was decided to skin test the patient with a broth filtrate of geotrichum. He was injected intradermally with 0.1 c.c. geotrichum broth filtrate in one arm, and the same amount of the uninoculated media in the other arm. He was positive with hard induration of 10 mm. to geotrichum while the control inoculation was negative. His entire family were all positive to geotrichum with induration ranging from 10 mm. to 20 mm. Treatment with potassium iodide was instituted. The lung fields cleared slowly with some residual pulmonary fibrosis and he recovered. These cases are to be reported in detail elsewhere.

CASE 5.—B. Y., aged 4 years, and a sister of Case 4, developed mild respiratory symptoms in June, 1947, at about the time her brother became ill. X-ray of the chest revealed enlarged hilar lymph nodes but no pulmonary infiltrations. Subsequent films taken during the next six months revealed pulmonary infiltrations in both lung fields similar to Case 4. During this time she had a mild cough, but appeared well. On Feb. 11, 1948, she began taking large doses of saturated potassium iodide and when seen on April 1, 1948, was perfectly well. An x-ray at this time showed complete clearing of the pneumonic process. A skin test with geotrichum antigen showed a 2 plus reaction, while other fungus antigens were negative. Nasopharyngeal smears and cultures were negative. A follow-up examination on Sept. 18, 1948, revealed a well child.

DISCUSSION

The object of the present study was to investigate the role of mycotic infections in respiratory tract diseases of children based on cutaneous, serologic, and mycological findings. A summary of the results obtained with skin test antigens in 211 children with various clinical findings is shown in Table I. The children were arbitrarily divided into three clinical categories: (1) those with pneumonia; (2) those with acute upper respiratory infections; and (3) a control group comprising children with no evidence of infectious disease.

As shown in Table I the results of the skin reactions of the three groups were essentially the same. The total positive reactors to the fungus antigens in the three clinical groups were 12.7 per cent, 9.7 per cent, and 11.8 per cent, respectively. Also no significant difference is seen if all children with respiratory infection (total 135) are compared with the control group. The incidence of positive reactors in the former is 11.1 per cent, while it is 11.8 per cent in the latter. Positive fungus skin tests were obtained only during the acute stage in

children with respiratory diseases. An average of 8 per cent of the children in the three groups had positive histoplasmin skin tests, and they ranged in age from 3 to 13 years. In this connection it is of interest that Bendenkopf and associates¹³ found that the histoplasmin sensitivity in university students resident of Chicago was 10 per cent for the age group 15 to 19 years.

Only about one-half of the children in the pneumonia group had clinical findings of pneumonia in addition to positive radiologic evidence. In this group no significant pathogenic bacteria were isolated in most instances. On the other hand, in most of the children with acute upper respiratory infections, the usual pathogenic bacteria such as beta hemolytic streptococci, coagulase-positive *Staphylococcus aureus*, pneumococci, etc., were isolated from nose and throat cultures.

Four children, representing the three categories, showed some cross reaction between histoplasmin and blastomycin. No false positive skin reactions were noted in individuals under penicillin or streptomycin therapy. It is of interest to note that only nine of the 211 children tested gave a history of allergy. Six of the allergic children were nonreactors. One was histoplasmin-positive and tuberculin-negative; one was positive to both histoplasmin and tuberculin, while the third was positive to blastomycin only.

Bunnell and Furcolow⁶ cited three cases in which skin sensitivity did not appear before the forty-sixth day after onset of illness. Twenty-five per cent of the negative reactors in our series who were given repeat skin tests after two weeks remained negative. In only about 15 per cent of the pneumonia group was it possible to do repeat skin tests six weeks to three months after the first test, and again the results were negative. Perhaps additional positives would have been found if it had been possible to carry out more repeat skin tests after a longer interval of time.

During the course of these studies three proved and two presumptive cases of fungus infection were demonstrated. The first was a case of primary histoplasmosis with clinical and x-ray findings of atypical pneumonia. This patient also had a positive complement fixation and skin tests for histoplasmosis. Tests for other fungus antigens were negative. *H. capsulatum* was isolated from blood drawn during the acute stage of this case and also from bronchial secretions. Case 2 was a fatal one of a child with granulomatous lesions of the lung and liver. An unidentified fungus isolated from the lungs was pathogenic for mice. Microscopic sections showed the presence of mycelia in the lungs of this child. In Case 3 *C. albicans* was isolated from an infant suffering from pneumonia and malnutrition. This patient had negative reactions to all fungus skin test antigens except Candida and recovered following dietary regulation and large doses of iodides. Although, as already mentioned, about 5 per cent of the nasopharyngeal cultures of the three groups studied were positive for *C. albicans*, and this species is known to be part of the normal throat flora, we feel that the finding of *C. albicans* in Case 3 was significant because this organism was isolated in predominant numbers repeatedly from the gastric lavage, bronchial secretions, and stool cultures. Furthermore, he had a positive skin test for

Candida only. Finally, he responded to large doses of iodides. Cases 4 and 5 were two siblings whose x-ray findings and clinical symptoms were similar to a case of geotrichosis previously described by one of us.⁷ These children showed a positive skin test for geotrichum filtrate and responded to iodide therapy although the lung fields cleared slowly with some residual pulmonary fibrosis. Skin tests with other fungus antigens were negative.

SUMMARY AND CONCLUSIONS

1. A survey to determine the incidence of systemic mycotic infections in acute respiratory diseases was done on 211 children. Each child was skin tested with various fungus antigens, and a nasopharyngeal culture was made for pathogenic bacteria and fungi. Fungus complement fixation tests as well as repeated bacterial and mycotic cultures of gastric lavage, bronchial secretions, and stools were carried out in selected cases with pneumonic involvement.

2. No significant difference was found in skin tests with histoplasmin, blastomycin, torulin, or coccidioidin in children with pneumonia, acute upper respiratory infections, or in the control group having no evidence of infectious disease. A total of sixty-three children with pneumonia were studied. Three were histoplasmin-positive and tuberculin-negative; one was histoplasmin-positive and tuberculin-positive; one was blastomycin-positive only; and one was blastomycin and tuberculin-positive. One was positive to geotrichum filtrate only and one to geotrichum filtrate and coccidioidin. Of the seventy-two children with upper respiratory infections, three were positive to histoplasmin only; three to histoplasmin and tuberculin, and one to torulin only. In the control group of seventy-six children, three were histoplasmin-positive only; four were positive to histoplasmin and tuberculin, and one was positive to torulin only.

3. Three proved cases of fungus infection were demonstrated: (1) a primary histoplasmosis with clinical findings of atypical pneumonia from which *H. capsulatum* was isolated during the acute stage; (2) a fatal infection with granulomatous lesions of the lung, liver, and kidney from which an unidentified fungus was isolated; and (3) *C. albicans* infection of the lung associated with malnutrition. Two presumptive cases of geotrichosis are described.

4. Although no significant correlation was found between systemic mycotic infections and acute respiratory disease in the present study, a fungus etiology should be considered in cases of atypical pneumonia because of the positive finding described.

REFERENCES

1. Aronson, J. D., Saylor, R. M., and Parr, E. I.: Relationship of Coccidioidomycosis to Calcified Pulmonary Nodules, Arch. Path. 34: 31, 1942.
2. Long, E. R., and Stearns, W. H.: Physical Examination at Induction. Standards with Respect to Tuberculosis and Their Application as Illustrated by a Review of 53,400 x-ray Films of Men in the Army of the United States, Radiology 41: 144, 1943.
3. Smith, C. E.: Coccidioidomycosis, M. Clin. North America 27: 790, 1943.
4. Christie, Amos, and Petersen, J. C.: Pulmonary Calcification in Negative Reactors to Tuberculin, Am. J. Pub. Health 35: 1131, 1945.
5. Palmer, Carroll E.: Nontuberculous Calcification and Sensitivity to Histoplasmin, Pub. Health Rep. 60: 513, 1945.

6. Bunnell, I. L., and Furcolow, M. L.: A Report on Ten Proved Cases of Histoplasmosis, Pub. Health Rep. 63: 299, 1948.
7. Kunstadter, R. H., Pendergass, R. C., and Schubert, J. H.: Broncho-pulmonary Geotrichosis, Am. J. M. Sc. 211: 583, 1946.
8. Milzer, A., and Levine, E. R.: A Rapid Mouse Test for Laboratory Diagnosis of Tuberculosis, Proc. Soc. Exper. Biol. & Med. 69: 16, 1948.
9. Littman, M. L.: A Culture Medium for Primary Isolation of Fungi, Science 106: 109, 1947.
10. Shaughnessy, H. J.: A Method for Producing Increased Carbon Dioxide Tension in Individual Culture Tubes and Flasks, J. Baet. 37: 153, 1939.
11. Tenenberg, David J., and Howell, Arden: A Complement Fixation Test for Histoplasmosis I and II, Pub. Health Rep. 63: 163, 1948.
12. Kunstadter, R. H., Whitecomb, F. C., and Milzer, A.: Primary Histoplasmosis with Recovery of *Histoplasma capsulatum* from the Blood and Bronchial Secretions. To be published.
13. Bendenkopf, W. G., Loosli, C. G., Lack, H., Rice, F. A., and Slattery, R. V.: Tuberculin, Coccidioidin, and Histoplasmin Sensitivity in Relation to Pulmonary Calculifications. A Survey Among 6,000 Students at the University of Chicago. Pub. Health Rep. 64: 17, 1949.

DIABETES MELLITUS IN CHILDREN

REVIEW OF 500 CASES

HENRY J. JOHN, M.D., F.A.C.P.
CLEVELAND, OHIO

THE diabetes seen in children may be considered to be a "pure" form of the disease, since it is uncomplicated by the degenerative changes which play a large part in the development of diabetes in older persons. Hence it is instructive to analyze the results in young patients after twenty-six years' experience with insulin treatment.

The series of 500 cases reported here has been observed over a twenty-seven-year period, so a few of them antedate the "insulin era." Some of these patients I have observed continually over many years. I have traced as many of the others as possible through correspondence with them or their families. I have no recent report on 136, or 27.2 per cent. Of the 364 patients traced, 303 are living and sixty-one are dead; i. e., 83.2 per cent of those traced are living and 16.7 per cent are dead.

INCIDENCE

The 500 cases of diabetes occurring in patients in the first two decades of life were observed in a total series of 6,000 diabetic patients (which I am reporting elsewhere). Thus, the incidence of patients under 20 years of age is 8.3 per cent. Fig. 1 shows the incidence by decades in the total series.

Age.—Diabetes mellitus may occur in a child at any age. In this series there were two children who were less than one year old when the disease appeared. Schwartzman and associates¹ collected from the literature and reviewed fifty-seven cases of diabetes mellitus in infants less than a year old. In the present series there were 263 instances in which the onset of diabetes occurred in the first decade and 237 in the second decade. Fig. 2 shows the incidence by years. This seems to indicate that the majority of cases of juvenile diabetes occur between the ages of 4 and 12 years. This finding may not be of statistical significance, but, owing to the rapid rate of growth during this period, it may be well to look for evidence in other series on this point.

Sex.—The sex distribution in this series of diabetic children was practically equal, as is true of other reported series (Table I). There were 255 (51 per cent) boys and 245 (49 per cent) girls. This finding is in definite contrast to the sex incidence of diabetes generally, as shown by my total series of 6,000 cases; among these patients of all age groups, the incidence in males was 43.3 per cent and in females 56.7 per cent.

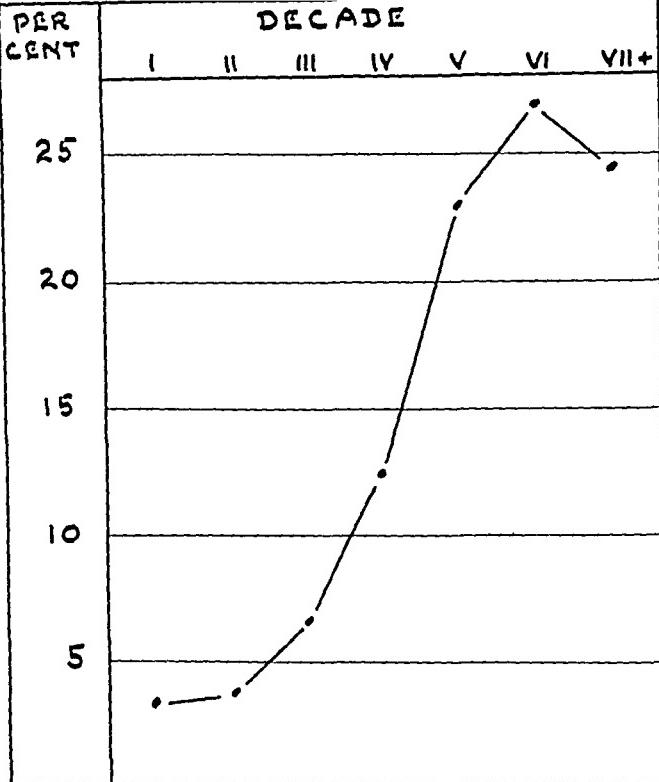


Fig. 1.—Age incidence (by decades) in 6,000 cases of diabetes mellitus.

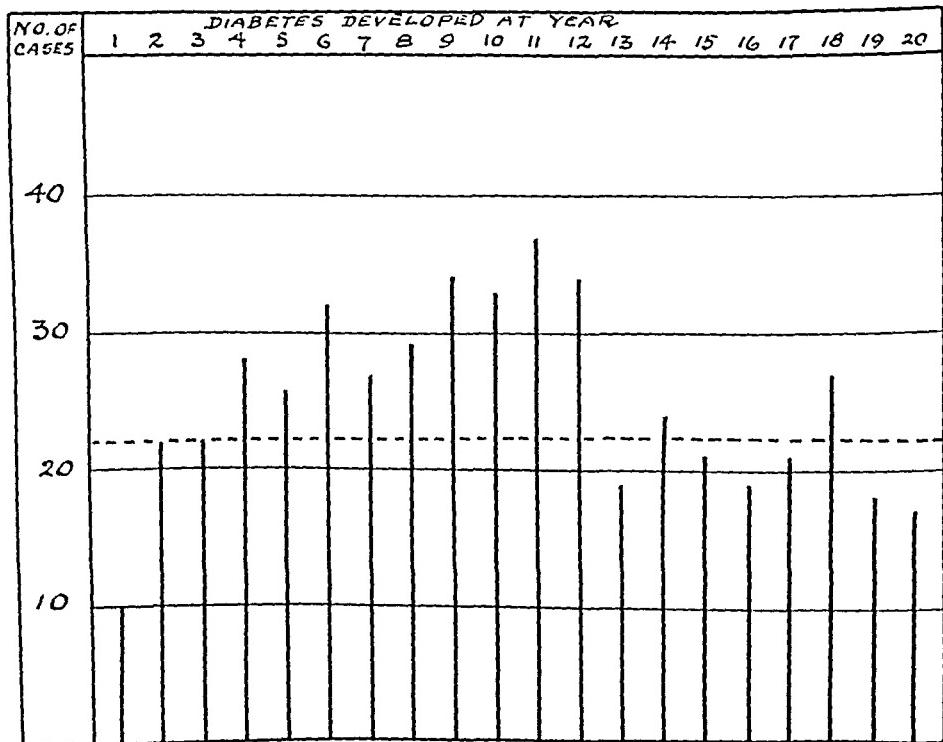


Fig. 2.—Age of development of diabetes in 500 children.

TABLE I. SEX INCIDENCE OF DIABETES IN CHILDREN

AUTHOR	NUMBER	PER CENT	
		MALE	FEMALE
Priesel and Wagner, ²	152	52	48
Pirquet ³	5,321	51	49
Joslin and White ⁴	750	50.4	49.6
Sundby ⁵	159	51	49
Total	6,382	50.9	49.1

TABLE II. THE HEREDITARY FACTOR IN 500 DIABETIC CHILDREN

CASES		PER CENT	
		MALE	FEMALE
No history obtained	73		
History obtained	427	100	
Gentile	381		89.2
Jewish	46		10.8
Hereditary history of diabetes	116	27.1	
Gentile	101		23.4 (of total group)
Jewish	15		26.4 (of Gentile group)
Familial history of diabetes	19	4.4	3.7 (of total group)
Gentile	18		33.5 (of Jewish group)
Jewish	1		4.2 (of total group)
Combined hereditary and familial history of diabetes	135	31.5	4.9 (of Gentile group)
Gentile	119		0.23 (of total group)
Jewish	16		2.2 (of Jewish group)
			27.6 (of total group)
			31.3 (of Gentile group)
			3.9 (of total group)
			35.5 (of Jewish group)

ETOIOLOGIC FACTORS

The two factors of prime importance in the etiology of diabetes in children are heredity and infection.

Heredity.—In the 500 cases, no history regarding hereditary or familial diabetes was recorded in seventy-three instances. Of the 427 cases in which the history was explicit in regard to this factor, there was diabetes in the hereditary background in 116. There was a familial history in an additional nineteen cases (Table II). The hereditary factor was approximately equal in the boys and the girls. The percentage of Jewish children in whom hereditary influences were present was somewhat higher than that of the group as a whole. Of the 427 children, forty-six were Jewish and there was a hereditary or familial history of diabetes in sixteen of these, or 35.5 per cent (as contrasted with 31.5 per cent for the entire group). My impression is that the influence of heredity may be more pronounced than is indicated by these percentage figures, since it has been my experience repeatedly that in children whose history showed no diabetes in the family at the time of onset, continuous follow-up has later revealed the presence of diabetes in some other member of the family. Hence I would venture to estimate the actual incidence of an hereditary tendency in diabetic children as about 40 per cent. The incidence as given by other

TABLE III. THE HEREDITARY FACTOR IN DIABETIC CHILDREN (OTHER AUTHORS)

AUTHOR	CASES	FAMILIAL AND HEREDITARY DIABETES (%)
Friese and Jahr ⁶	60	11.6
Toverud ⁷	47	17
Lion and Moreau ⁸	100	23
Priesel and Wagner ²	108	27
Host ⁹	50	30
Ladd ¹⁰	35	37
Joslin and White ⁴	750	40
Schwartzman et al. ¹	28	43
Collens and Grayzel ¹¹	10	50
Smyth ¹²	31	54

TABLE IV. THE FACTOR OF INFECTION IN 500 DIABETIC CHILDREN

TYPE OF INFECTION	TIME OF ONSET OF DIABETES FOLLOWING INFECTION						UNDER 1 YEAR	NOT STATED	TOTAL
	DAYS								
	1-10	11-20	21-30	31-40	41-50	51-60			
Mumps	5	1	2			1	3	25	37
Influenza	9	7	7	2		5		3	33
Measles	2	1	2	1		1	2	2	11
Dysentery	1	1	1					2	6
Pneumonia			4		1		3	2	10
Intestinal toxemia								3	3
Boils	1	1	1						3
Tonsillitis	1	1		1		1			4
Nephritis								2	2
Glandular fever			2		1				3
Jaundice	2	1							3
Septic endocarditis								1	1
Poliomyelitis			1						2
Abscessed teeth				1					1
Infections (nonspecific or unknown type)	1	1	1					23	26
Pyelitis				1				1	2
German measles	1								1
Scarlet fever	2	1	1					1	5
Mastoiditis			1					1	2
Whooping cough		1	1			1	1		4
Chicken pox	2		2						4
Otitis media			1						1
Total	27	16	27	6	2	9	10	67	164

authors reporting on small series varies from 11 to 54 per cent (Table III). Joslin and White,⁴ who reported a series of 750 cases, found the incidence to be 40 per cent.

Infection.—Infections of various types play a definite role in the causation of diabetes in children, as has been amply demonstrated in literature on this subject.¹³ The common observation of the onset of diabetes within ten to thirty days following various childhood infections certainly furnishes presumptive evidence that the infections were a factor of importance in the development of these cases. In the present series of 500 cases, there was a history of recent infection in 164 instances (Table IV). In eighty-seven, the diabetes appeared within sixty days after the infection; in ten, within one year, and in sixty-seven, the exact time of onset in relation to the infection was not stated. Thirty-seven cases developed following mumps and thirty-three after influenza.

There were twenty-six cases after infections of nonspecific or unknown type. Other infections which were followed by diabetes in this series were measles, dysentery, pneumonia, intestinal toxemia, boils, tonsillitis, nephritis, glandular fever, infectious jaundice, septic endocarditis, poliomyelitis, abscessed teeth, pyelitis, German measles, scarlet fever, mastoiditis, whooping cough, chicken pox, and otitis media. The time of onset and the distribution of cases following these infections are shown in Table IV.

The presence of a history of recent infection in 164 cases (32.8 per cent) in this series is in keeping with the observations of other authors, some of whom report a higher percentage. Friese and Jahn⁶ stated that in nearly three-fourths of their series of sixty diabetic children they could demonstrate that diabetes developed shortly after an infection. Fischer¹⁴ reported that the onset of diabetes in his series was immediately traceable to infection in approximately 35 per cent of the cases. Landabure and Magdalena¹⁵ showed that acute infectious diseases had preceded diabetes within ninety days in 23 per cent of their cases. Adams¹⁶ called attention to the fact that the incidence of diabetes mellitus increases in the fall, winter, and spring, when infections are most common. Jones¹⁷ reported a high incidence of cases of diabetes following an influenza epidemic.

In the present series, the largest number of cases of diabetes following a particular infection was that related to mumps. Pancreatitis which occurs as a complication of parotitis has been reported frequently in the literature, and in a proportion of these cases diabetes is the eventual result. I have seen several such cases in adults, as well as in the children reported here. Among the authors who have reported cases of diabetes after parotitis are Gilhespie and Holden,¹⁸ Jacob,¹⁹ Harris,²⁰ and Fischer.¹⁴

The fact, as shown in this series, that diabetes in children develops after many types of infections, is amply corroborated by numerous reports by other authors of the onset of diabetes following various infectious diseases. Among these reports are the following: after acute colds, tonsillitis, and influenzal infections, Lierle and Porter,²¹ Wendt and Peck,²² Jones,¹⁷ after purpura, Lefkowitsch;²³ after pyelitis, Smith;²⁴ after hepatitis and jaundice, Sweeney and Shirley,²⁵ Brems,²⁶ Freund and Marchand,²⁷ after malaria, Rau²⁸ and after diphtheria, Hector.²⁹ Numerous authors have called attention to the disturbance of carbohydrate metabolism that occurs during or after encephalitis or poliomyelitis. Kasanin and Grabfield,³⁰ in a study of seventeen cases, concluded that there was a fundamental disturbance of sugar metabolism in epidemic encephalitis and that this derangement persisted in patients suffering from mental sequelae of the disease. Similar conclusions have been reported by McCowan,³¹ Brugsch, Dressel, and Lewy,³² Aschner,³³ Karplus and Kreidl;³⁴ Nordmann³⁵ reported hyperglycemia in poliomyelitis and Schwartzman and associates¹ found diabetes associated with neuropathy in six of forty-eight cases. A few authors have attempted to show a relationship between syphilis and diabetes, but the general consensus is that syphilitic infections are of no significance as an etiologic factor in diabetes. In this series there was no case in which syphilis could have been a predisposing factor.

MECHANISM OF INFECTION IN PRODUCTION OF DIABETES

The question is unanswered as to why infection precipitates diabetes in one child and does not do so in ninety-nine others. Is it that the child who becomes afflicted with diabetes had a decreased insulinogenic reserve which was exhausted by the added strain of the infection? Is it that in the individual instance in which diabetes appears, the particular predisposing infection caused a more virulent toxemia than in the usual case? Perhaps both of these factors, and others not yet recognized, are important.

One fact that is well established is that infection affects the function of the pancreas adversely. In a diabetic child whose condition is well under control, for example, on a dosage of 20 units of insulin daily, a febrile condition may so upset the picture that the dosage must be increased to 80 units to control the hyperglycemia. Knowing that this is true in the diabetic child, it is easy to imagine a similar situation (and there is clinical and experimental evidence to support this assumption) in the nondiabetic child during an infection.

The possibilities usually considered to explain the decreased sugar tolerance during an infection, both in diabetic and nondiabetic individuals, are: (1) reduced insulin output or a prior decreased insulinogenic reserve; (2) inability of the liver to store glycogen readily; (3) interference with the action of insulin; (4) derangement of the mechanism of nervous control of sugar metabolism; (5) an increased output of epinephrine or of pituitary secretion which inhibits the effect of insulin. Opinions differ considerably as to which of these factors is mainly responsible, alone or in combination. It would appear to me that interference with the action of insulin, either by toxic products or by increased secretion of suprarenal or pituitary hormones antagonistic to insulin, is the most likely probability. If the liver damage were of prime importance, hyperglycemia would be encountered more frequently; furthermore, in patients with marked cirrhosis of the liver there is no hyperglycemia. Labb   and Boulin³⁶ in a study of nondiabetic patients during acute infections, found alimentary glycosuria in 75 per cent. The disturbance in glucose regulation did not parallel the severity of the infection, and there was no sign of insufficiency of liver function. They stated: "It is possible that recurrences of this transient disturbance of glucose balance create a true diabetes more frequently than believed." Lawrence³⁷ suggested, on the basis of experimental and clinical evidence, that toxins and infections antagonize insulin action by the stimulation of the thyroid and suprarenal glands. A contrary opinion has been stated by Fukuda and Itabashi;³⁸ they believe that hyperglycemia during infection in febrile diseases is caused by the action of bacterial toxins on the central control mechanism and not by peripheral action on the suprarenals and on the liver.

Although many questions remain as to the mechanism of the influence of infection on development of the diabetic state, the evidence, both clinical and experimental, that the carbohydrate metabolism is disturbed during infections is quite conclusive. A typical report is that of Williams and Dick,³⁹ who studied the carbohydrate metabolism in 108 patients with infections such as scarlet fever, diphtheria, pneumonia, influenza, measles, erysipelas, encephalitis, mumps,

epidemic meningitis, poliomyelitis, and acute tonsillitis, and in twenty-nine rabbits and three dogs in which infections were produced experimentally. Temporary glycosuria occurred in 41 per cent of the animals, in six animals this decreased tolerance lasted for several weeks or months and required treatment. The animals also showed an increased amount of dextrose in the urine during the period of acute infection. Necropsies on the animals that died revealed microscopic evidence of degeneration in the islets of Langerhans.

In view of the large number of cases of diabetes which occur in children after infections, it would be well for pediatricians to examine the urine for sugar once a week for four to six weeks after such an illness. If this were done, diabetes would be discovered early in many instances, with great advantage to the children concerned. In the earliest stage, the process affecting the islands of Langerhans may still be reversible, whereas in later stages it becomes irreversible and the pancreatic damage becomes permanent. The earlier the recognition of the insulinogenic weakness, the better the chance to control the condition and prevent additional damage.

MANAGEMENT OF DIABETIC PATIENTS DURING ACUTE INFECTIONS

The two cases which follow illustrate the importance of adequate protection of the diabetic child during intercurrent infections.

CASE 1.—Fig. 3 shows the course of the diabetes and the treatment required for its control in a patient who contracted the disease at the age of 8 years. With adequate treatment, the diabetic condition improved sufficiently that all insulin could be discontinued. He presented a normal fasting, noon, and evening blood sugar and was sugar-free on diet alone on repeated examinations. Then he contracted measles. He lived in a small town and his physician did not appreciate the change in the glucose metabolism caused by the infection and did not reinstate insulin during this period. When I saw him a few weeks later, the blood sugar had increased to almost 500 mg. per cent and he displayed signs of severe acidosis. Insulin had to be reinstated, and in large doses, and now, nearly eighteen years later, he is still required to take large quantities of insulin because of the inadequate management of the diabetes during the acute infection. This apparently caused permanent damage which is irreversible.

CASE 2.—In this instance (Fig. 4), the infection and its subsequent aggravation of the diabetes were properly considered and managed. This boy was 7½ years old in 1936 when he first developed diabetes. At the beginning, the blood sugar was high morning, noon, and night, and insulin had to be increased up to 50 units daily. After a month and one-half, all insulin could be discontinued for a period of three months, during which the three antecibal blood sugars were normal. After this, insulin had to be resumed, and in 1938, at the age of 9½ years, he was taking 10 to 18 units of insulin and 12 to 15 units of protamine zinc insulin a day. At that time he had mumps. With increased insulin dosage (to 40 units), there was only slight elevation of the blood sugar. Afterward, the dosage was reduced to 30 units. Six years later he had a second attack of mumps. By this time his diabetes had increased in severity (possibly owing to dietary indiscretion) and he was taking 150 units of insulin daily. However, the onset of the infection required only a minimal increase in the insulin dosage. The blood sugar during the infection and two years later showed reasonable control of the diabetic condition, since two out of three determinations were at or near the normal level.

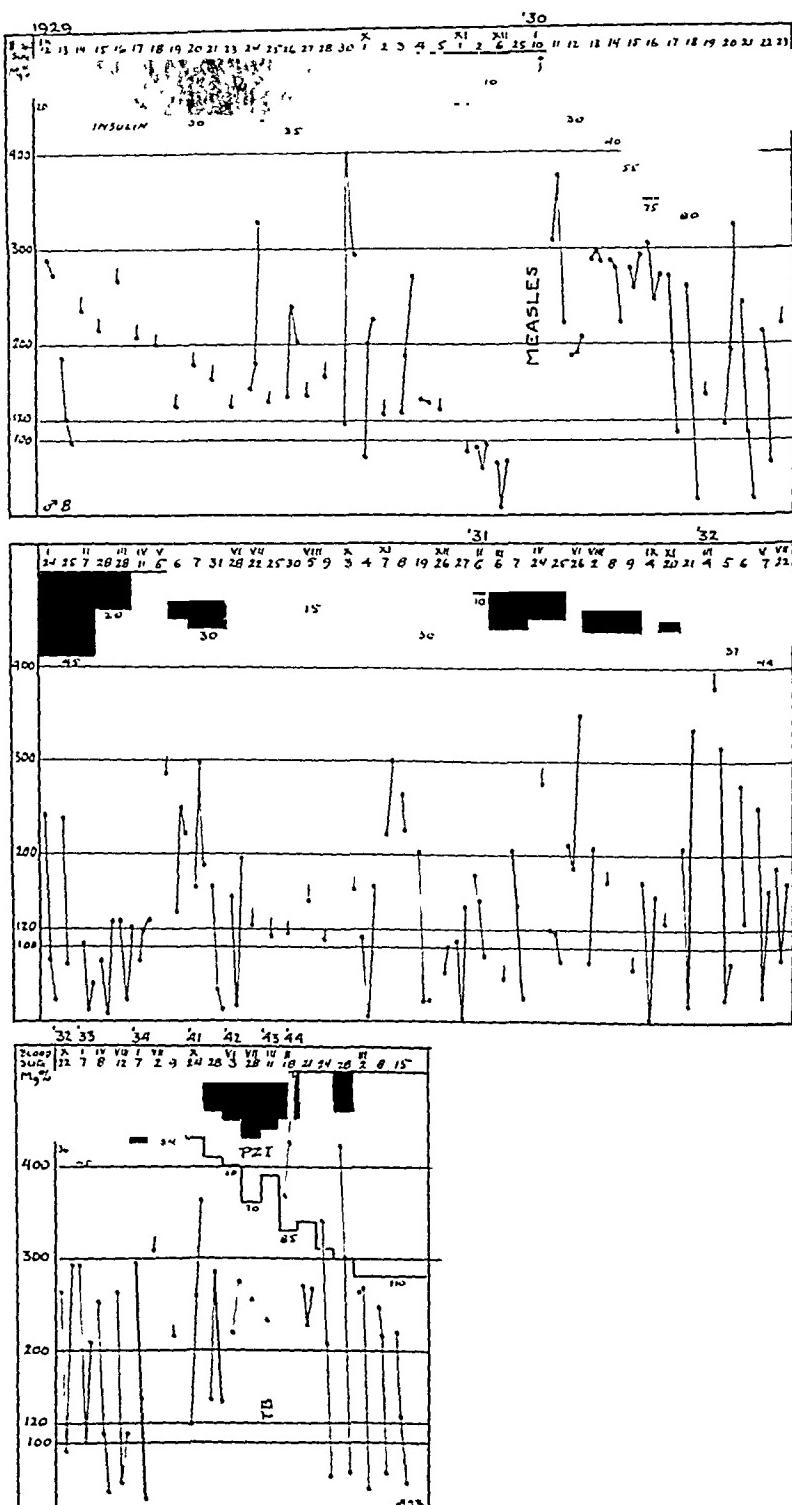


FIG. 3.—Effect of infection (measles) on the diabetic status in a boy aged 8 years.

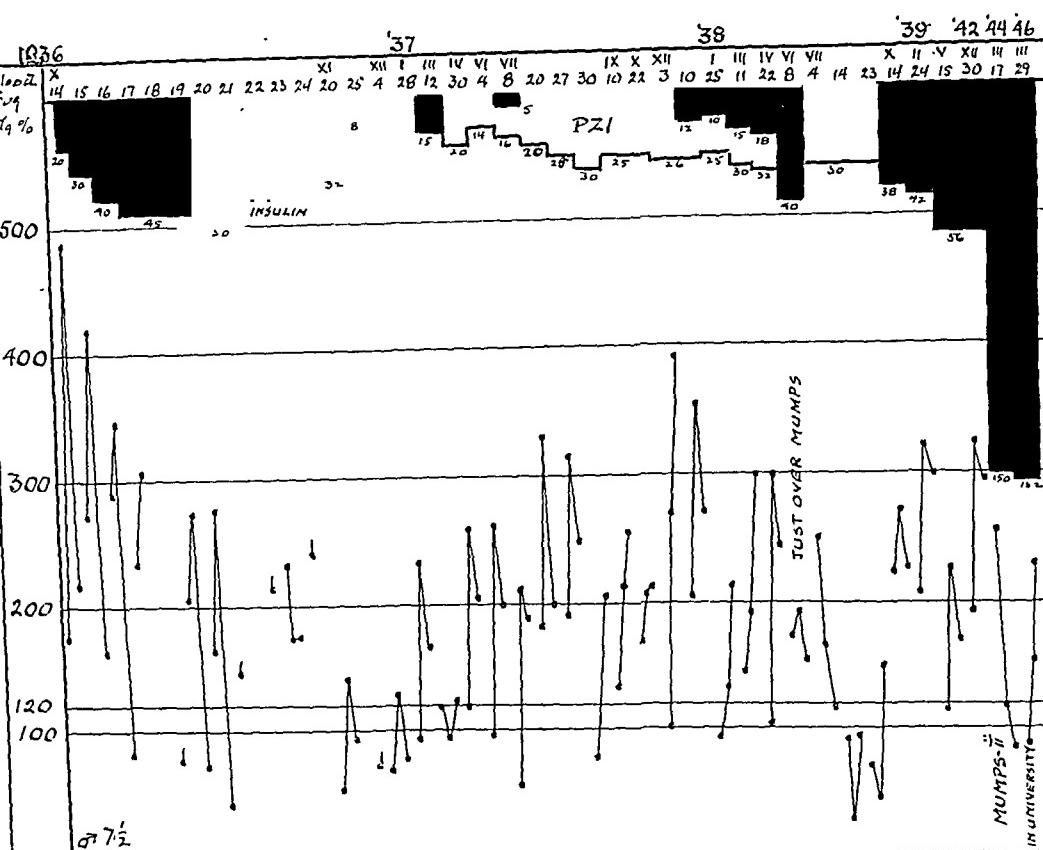


Fig. 4.—Effect of infection (mumps) on the diabetic status in a child, aged 9½ years, when counteracted by adequately increased insulin dosage.

CONTRAST OF ETIOLOGIC FACTORS IN ADULTS AND CHILDREN

As already stated, heredity and infection apparently are the most important etiologic factors in juvenile diabetes; whereas in older patients obesity and degenerative diseases obviously play a predominant role. This is clearly shown in the ensuing discussion of glucose tolerance tests, obesity, circulatory disorders, and hyperthyroidism in groups of children and of adults.

Glucose Tolerance Tests in Children and Adults in Various Affections.—In 1934, I published a series of 192 glucose tolerance tests⁴⁰ performed on patients under 20 years of age. Some of these tests were made for diagnostic reasons, others purely for scientific information. It seems pertinent here to recapitulate the results of this study, which are shown in Table V. In this group of juvenile individuals, 81.7 per cent showed normal glucose tolerance curves, whereas in a group of 1,535 adults subjected to a similar study, normal curves were obtained in only 61.5 per cent. Fig. 5 shows graphically the trend of normal and diabetic curves of glucose tolerance according to age in the total series of 1,727 cases. This chart corroborates the information shown in Fig. 1 on the age incidence of diabetes. The findings in regard to the increased incidence of

TABLE V. GLUCOSE TOLERANCE TESTS IN 192 CHILDREN

CLINICAL CONDITION	GLUCOSE TOLERANCE		PER CENT		TOTAL TESTS
	NORMAL	DIABETIC	NORMAL	DIABETIC	
Obesity	12	2	86	14	14
Hyperthyroidism	14	3	82	18	17
Hypothyroidism	10		100		10
Hypopituitarism and dwarfism	40	4	91	9	44
Glycosuria	35	17	67	33	52
Hyperglycemia	1		100		1
Arthritis and rheumatic disease	5	4	56	44	9
Eye affections	19	3	87	13	22
Neuropathies	6	1	85	15	7
Hyperpituitarism	1	1	50	50	2
Raynaud's disease	1		100		1
Tuberculosis	3		100		3
Skin diseases	4		100		4
Glycosuria of pregnancy	1		100		1
Cholelithiasis	1		100		1
Hypogonadism	1		100		1
Duodenal ulcer	1		100		1
Normal	2		100		2
Total	157	35	82	18	192

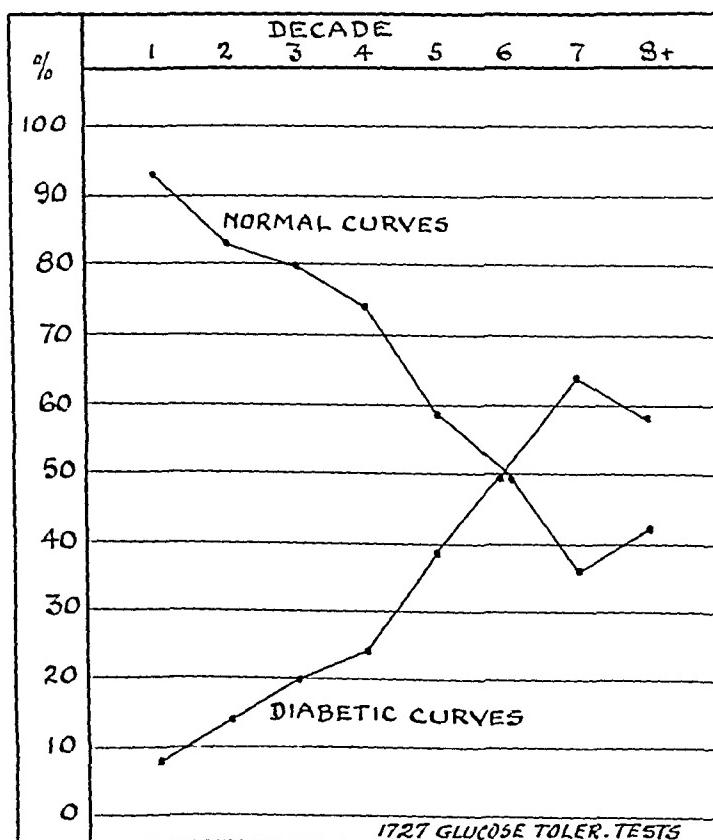


Fig. 5.—Incidence of abnormal (hyperglycemic) curves in 1,727 glucose tolerance tests, showing the increase with each successive decade of life.

diabetes with age suggest that this condition is largely a degenerative disease resulting from various affections, endocrine disturbances, infections, arteriosclerosis, and senescence.

The contrast in the incidence of diabetic-type glucose tolerance curves in adults and children is quite striking. In patients with obesity and hyperthyroidism, for instance, there were about three times as many diabetic curves in adults as in children. In the presence of glycosuria, rheumatism, and hypopituitarism, the incidence of diabetic curves was about the same in the two groups. In rheumatic conditions and chronic infections both groups showed a high incidence of abnormal curves. These differences apparently reflect functional differences between the child and the adult. The child apparently is a better physiologic unit than the adult who has been subject to repeated infections, functional stresses and strains, and dietary abuses, and thus has exhausted much of his initial insulinogenic reserve. Any intercurrent strain imposed on such a background produces greater damage than when the physiologic background is intact.

Heredity and Infection.—As has already been pointed out, heredity and infection seem to be the most important etiologic factors in diabetes in children. As shown in Table II, there was a history of hereditary or familial diabetes in 31.5 per cent of this group of children, whereas in a series of 6,000 cases, including both adults and children, the incidence of the hereditary factor was 19.13. This indicates that heredity is a much more important factor in juvenile diabetes than it is in adults with the disease. The same is true of infection, although the actual role of infection is more difficult to assess in adults. The appearance of diabetes following an acute infection is by no means rare in adults, though a history of this type is much less frequently encountered than is the case with children. In adults who have had repeated acute or chronic infections it is difficult or impossible to say how much of the general physiologic breakdown which forms the background for the development of diabetes is attributable to this cause. That it is not negligible is suggested by the fact that the incidence of abnormal glucose tolerance curves is much higher, both in adults and children, in patients with rheumatic conditions or chronic infections than it is among patients in general.

Obesity.—Obesity is not the prominent factor in the causation of diabetes in children that it is in adults, although even in very young patients it cannot be completely ignored. Fig. 6 shows the percentage incidence of abnormal, or hyperglycemic, glucose tolerance curves in adults and in children with obesity. Not all of these patients have or will have frank diabetes, but the abnormal carbohydrate metabolism represents a warning signal that the disease may develop if the obesity remains uncontrolled. This is corroborated by the strikingly similar incidence of a history of obesity in diabetic patients. In a series of 2,970 diabetic patients of all ages in whom this factor was determined definitely, it was found that 33.9 per cent were and always had been of normal weight, or at most no more than 10 per cent above normal. Conversely, 66.1 per cent were or had been at some time 11 to 220 per cent overweight. Anders and

Jameson⁴¹ reported a series of 1,306 cases of obesity in which they found that 119, or 9.1 per cent were diabetic. Since the incidence of diabetes in the general population is, at most, no more than 2 per cent, this represents a greatly increased incidence (approximately five times the usual) in the obese.

Fortunately, because degenerative influences have not been at work over a sufficiently long period in children, overweight does not have the same coincidence with diabetes that it has in adults. Nevertheless, in 1920, Mouriquand⁴² called attention to the fact that obesity or a familial history of obesity cannot be ignored in considering the problem of juvenile diabetes. He warned that incipient diabetes might be detected in children of the obese, the diabetic, and also arthritic and gouty parents. He stated that nearly all of his patients with early inherited obesity developed diabetes before the age of 40 years, but that when obesity did not develop until later in life, only 50 per cent became diabetic. In contrast to this inherited type of obesity, only 15 per cent of patients with acquired obesity developed diabetes.

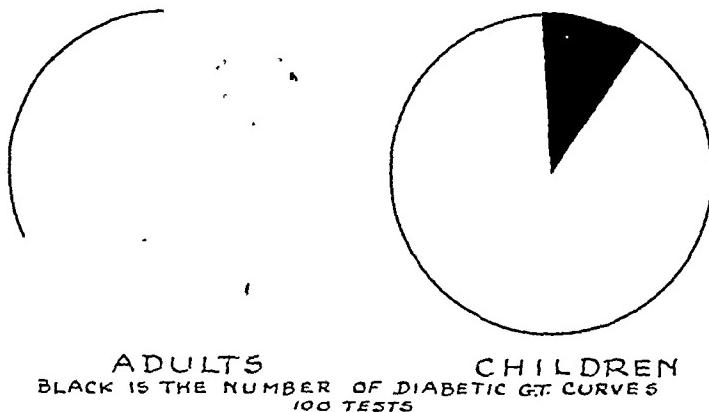


Fig. 6.—Incidence of abnormal (hyperglycemic) curves in glucose tolerance tests on obese patients, showing that the percentage is much higher in adults than in children.

Despite the relative rarity of obesity in diabetic children, it is nevertheless wise from the clinical standpoint to look upon the overweight child with suspicion and to assess carefully the carbohydrate metabolism in such individuals. The treatment of obesity in children depends, of course, on the underlying cause, which is often glandular. The problem of the prevention or control of obesity in children presents a fertile field for investigation in pediatrics and perhaps might prove to be significant from the standpoint of public health in pointing the way toward understanding and control of degenerative diseases later in life.

Arteriosclerosis.—In children, arteriosclerosis does not precede diabetes as it often does in older individuals, and for that reason cannot be considered as an etiologic factor in juvenile diabetes. Pearl Zeek⁴³ searched the medical literature for the past 100 years and found but ninety-eight cases of juvenile

arteriosclerosis, excluding those resulting from syphilitic infections, and, so far as could be determined, none of these children with arteriosclerosis had diabetes.

Although arteriosclerosis is not an etiologic factor in diabetes in children, it is a complication of this condition. After children have had diabetes ten years or more, arteriosclerosis begins to appear in a large proportion of cases. The literature brings out more evidence of this with each passing year. White⁴⁴ reported a series of 220 cases of juvenile diabetes in which the incidence of vascular disease in those who had had diabetes twenty years or more was 92 per cent. The vascular changes in young diabetics lead to diabetic retinitis with hemorrhages and intercapillary glomerulosclerosis, both of which are extremely serious conditions. I am not in a position to give statistical data on the incidence of arteriosclerosis in this series of children, since this requires systematic, periodic, roentgenologic study. I started such a survey, but when I entered private practice it had to be abandoned because of the cost to the patient. However, in the patients that I have followed consistently over a period of years, at least 50 per cent have developed arteriosclerosis and many of them have had the more serious sequelae, such as blindness and renal failure.

Hyperthyroidism.—Some years ago I analyzed 9,000 cases of hyperthyroidism⁴⁵ and found that 38.6 per cent of these had glycosuria and 6.88 per cent had nonphysiologic hyperglycemia (either fasting or two and one-half hours or more after meals). The patients with hyperglycemia were closely watched and protective treatment with insulin was administered. Despite this, 186 of the 620 patients remained permanently diabetic. This represented an incidence of diabetes in the 9,000 cases of 2.1 per cent. Without the protection afforded by diet and insulin during the hyperthyroidism, I believe the incidence of permanent diabetes in this group would have been much higher.

In the case of children, abnormal (diabetic-type) glucose tolerance curves occur only about one-fourth as frequently in hyperthyroidism.⁴⁶ Apparently the greater physiologic reserve or flexibility seen in the presence of other conditions, such as obesity, in the young, can withstand the grave metabolic derangement seen in hyperthyroidism and still right itself when the acute strain has been removed. In my own series of children with hyperthyroidism who were protected during and after the acute stage of the disease, none developed a frank and lasting diabetes. However, two children with slight derangement of carbohydrate metabolism during the acute stage of hyperthyroidism were told by the surgeon to forget about the hyperglycemia after thyroidectomy; both returned later with frank diabetes and are under treatment to this day.

On the whole, hyperthyroidism plays an insignificant part in the production of diabetes in children. However, when abnormalities in carbohydrate metabolism are found in the presence of juvenile hyperthyroidism, these cannot be safely disregarded, as the two cases just cited show. In fact, no matter what its cause, hyperglycemia should never be disregarded as insignificant.

TABLE VI. DURATION OF MARRIAGES IN 300 LIVING CHILDREN

MORTALITY

Of the present series of 500 cases, I have been able to trace fully 364 cases, or 72.8 per cent. Of these, 303, or 83.2 per cent (of those traced) are living, and sixty-one, or 16.7 percent, died during the twenty-seven-year period of the study. Of the 303 living patients, 41.25 per cent have been followed ten years or less since the onset of the diabetes, 43.23 per cent have been followed from ten to twenty years, and 15.51 per cent have been observed for more than twenty years. A detailed analysis of these cases, according to the age at which diabetes developed, sex, and the length of survival to the present, is shown in Table VI.

In considering the sixty-one deaths in this series, it must be remembered that some of these cases date back to about two years before the use of insulin, a fact that influences the number of deaths from coma. Many of the children died in their homes in small towns, where facilities were not available for adequate treatment. Table VII shows the causes of death in this series. It is clear that coma ranks first as a cause of death in diabetic children. The second most frequent cause of death was kidney involvement which I called intercapillary glomerulosclerosis. This diagnosis was confirmed in some of these cases by necropsy; in others it was based on clinical evidence of diabetes of long duration, retinal sclerosis and hemorrhages, albuminuria, and edema.

TABLE VII. CAUSE OF DEATH IN 61 CHILDREN

CAUSE	NO. CASES
Diabetic coma	31
Intercapillary glomerulosclerosis	11
After surgery	5
Tuberculosis	4
Accident	3
Uremic coma	1
Aspiration of foreign body	1
Pneumonia	1
Meningitis	1
Ruptured appendix	1
Septicemia	1
Unknown	1
Total	61

Table VIII shows the length of time that these sixty-one diabetic children lived from the onset of their diabetes until death. The highest mortality rate was in the first year of the disease. Eighteen children, or 29.5 per cent of the sixty-one who died, succumbed within a year of onset of the diabetes. If a mother can see her child through the first year, the immediate threat to his life caused by the diabetes is greatly lessened. The initial period of adjustment to the diabetic condition and its involved problems is by far the hardest for all concerned—the patient, the family and the physician. The commonest mistake made by the family, and even by some physicians, when a diabetic child becomes ill and cannot retain food, is to withhold food and insulin, with the result that he goes into coma.

DURATION OF DIABETES BEFORE DEATH IN SIXTY-ONE CHILDREN

COMPLICATIONS

Coma.—The most serious complication and threat to the life of the diabetic child is coma resulting from acidosis. Thirty-one of the sixty-one deaths in this series were caused by this condition, representing 8.5 per cent of the 364 patients traced, or 6.2 per cent of the entire series of 500 cases.

In 1934, I reported my studies on diabetic coma in a series of 218 diabetic children.⁴⁶ In this series, covering a period of fourteen years, there were fifty instances of diabetic coma (23 per cent). Thirty-one of these children were under my immediate care during the coma; nineteen were cared for by family physicians, chiefly in small towns. Of the thirty-one patients under my care, five died; three of these were moribund on arrival and died within one hour after admission to the hospital. One died during the preinsulin period. Of the nineteen children cared for by other physicians, sixteen died and three survived. Thus the total mortality in the group I cared for was 16.1 per cent, and if the four patients just mentioned are excluded, only 3.2 per cent. The mortality in the group cared for by family physicians was 84.2 per cent. It must be remembered that these results were obtained in the early years of the use of insulin at a time when physicians were not well acquainted with this drug and were afraid to use it in large quantities.

In the years since the period covered by this earlier study, coma occurred in twenty-seven children of the present series (between 1934 and 1948). Of these, twenty-three were under my care during the emergency and four were managed by other physicians. Of the twenty-three, only one died (Table IX). Two of the four children cared for elsewhere succumbed.

TABLE IX. INCIDENCE OF DIABETIC COMA IN 500 CHILDREN

	1920-1934		1934-1948	
	CASES	PER CENT	CASES	PER CENT
Total diabetic children	218	100	282	100
Coma	50	23	27	9.5
Under personal care	31		23	
Died	5*	16.1	1	4.3
Under care of family physician	19		4	
Died	16	84.2	2	50.0

*One treated in pre-insulin era; three moribund on admission and died within one hour.

These figures reflect the picture in regard to diabetic coma in children during the last twenty-eight years. The results show that the quality of medical care during this emergency has improved tremendously, but still is not all it could be. The chief reasons for the failures are inadequate dosage of insulin and failure to use sodium chloride and glucose solutions in large quantities. Failure to handle the emergency of diabetic coma adequately in the early days of insulin use was excusable; knowledge of it was incomplete, and many physicians were timid in handling it. However, this excuse is no longer tenable, and it is significant that the two deaths in the four cases handled by other physicians in the later series occurred in one of our best hospitals, where all the facilities for adequate treatment were available. One of the reasons for in-

efficient treatment in a hospital is delay in getting the laboratory reports. The results of determination of blood sugar should be available in thirty minutes, for the test requires only twenty minutes. Blood sugar determinations on a patient in diabetic coma should take precedence over routine laboratory work, for the regulation of the insulin dosage in these cases is literally a matter of life or death. A patient in coma should never be left to the care of assistants or students. The physician responsible should take personal charge of the case and show his assistants how to proceed resolutely in the emergency, on the basis of confidence resulting from much experience.

Intercapillary Glomerulosclerosis.—The diagnosis of intercapillary glomerulosclerosis in this series was based largely on clinical evidence, although this was confirmed by necropsy in a few cases. Henderson and associates¹⁷ performed post-mortem studies in a large series of diabetic patients with glomerulosclerosis accounting for 19 per cent of the deaths. In correlating their pathologic findings with clinical data, they suggested that a presumptive diagnosis of glomerulosclerosis should be based on the following factors: (1) diabetes of long standing, (2) albuminuria, (3) hypertension, (4) renal insufficiency, and (5) mixed vascular and diabetic retinopathy. Glomerulosclerosis is but rarely associated only with diabetes and albuminuria, according to these authors. Using these criteria, the evidence justified the diagnosis of intercapillary glomerulosclerosis in eleven of the sixty-one deaths in this series (18 per cent of the deaths; 3 per cent of the 364 cases traced).

The optimistic attitude that prevailed for nearly two decades after the introduction of insulin concerning the treatment of the diabetic child has, in recent years, been tempered considerably by the disconcerting reports regarding the incidence of arteriosclerosis and its serious complications in young diabetics who have had the disease ten years or longer. The future for these patients looks considerably less bright than it did ten years ago. White and Waskow¹⁸ reported 220 juvenile diabetics who had survived twenty years or more since the onset of the disease. Of this group, 203, or 92 per cent, had vascular disease. Two had had a cerebral vascular accident; seven had coronary insufficiency; forty showed albuminuria; fifty-five had hypertension; seventy had calcified arteries; seventy-five had retinal hemorrhages; eighty-five had retinal arteriosclerosis, and six had retinitis proliferans. These authors also reported: "Since 1940 every diabetic child in our clinic who has survived fifteen years of diabetes and has come to autopsy has shown this lesion (intercapillary glomerulosclerosis), with or without pyelonephritis." Dolger¹⁹ reported that of 200 patients subjected to regular periodic examinations, 50 per cent showed albuminuria at the time that retinopathy developed. In a group of sixteen patients who developed diabetes before the age of 10 years and in thirty-nine who developed diabetes between the ages of 10 and 20 years, all of whom had had diabetes for twenty-five years, Dolger found retinitis with hemorrhages in all.

Although I have not been able to follow personally all of the patients in this series by regular periodic examinations, I do have data on the incidence of albuminuria in a group of eighty-three patients who have continued under my

personal care over a period of years. Twenty-six (31.3 per cent) of these show albuminuria, and fifty-seven (68.7 per cent) do not. The incidence of albuminuria relative to the duration of the diabetes is shown in Table X. The interesting thing here is that the percentage incidence of albuminuria did not increase appreciably with longer duration of the diabetes, a finding somewhat at variance with the reports of others.

TABLE X. APPEARANCE OF ALBUMINURIA IN EIGHTY-THREE DIABETIC CHILDREN

DURATION OF DIABETES IN YEARS	CASES	ALBUMINURIA		NO ALBUMINURIA	
		CASES	PER CENT	CASES	PER CENT
10 or less	31	9	29	22	71
10 to 15	31	11	35.4	20	64.6
16 to 20	18	6	33.3	12	66.7
21 to 25	3	0		3	100.0
Total	83	26	31.3	57	68.7

Other Complications.—Diabetic coma and glomerulosclerosis accounted for slightly under 70 per cent of the sixty-one deaths in the present series. The other deaths resulted from surgical operation, some type of infection, or accident. Diabetes represents an additional risk in case of surgery, but if the diabetic status is carefully watched and managed during the emergency, with proper regulation of the insulin dosage according to the indications, the results are generally satisfactory. The five deaths after operation in this series are largely accounted for by the fact that the surgery was performed in small hospitals where adequate facilities for emergency management of the diabetes were lacking. There is also the possibility that two of these patients actually had diabetic coma, rather than the acute appendicitis for which operations were performed. Since the onset of diabetic coma is marked by nausea and vomiting, this diagnostic mistake is not rare among physicians without great experience in treatment of diabetes.

The importance of thorough study of the carbohydrate metabolism and its fluctuations during any intercurrent infection has already been stressed. If these sudden changes are not properly controlled, infection may be a precipitating cause of diabetic coma. In any infection in a diabetic child, there is danger of a permanent decrease in the insulinogenic reserve unless adequate protection is given at such a time.

SUMMARY

The present study reports an analysis of 500 cases of juvenile diabetes (onset of the disease during the first two decades of life) in a total series of 6,000 diabetics observed during a period of twenty-seven years. Thus the incidence of diabetes in patients 20 years of age or less was 8.3 per cent. The sex distribution in the 500 cases of diabetes in children was practically equal, with 255 (51 per cent) boys and 245 (49 per cent) girls.

Heredity and infection are evidently the prime etiologic factors in the development of juvenile diabetes. In this series there was an hereditary or familial history of diabetes in 31.5 per cent, with the incidence in forty-six Jewish children of the group somewhat higher, i. e., 35.5 per cent. Infections,

principally the acute exanthemata, play a considerable role in precipitating the onset of diabetes. In this group of 500 cases, there was a history of antecedent infection in 164. In the majority of these, the diabetes appeared within two months after the infection.

A comparison of glucose tolerance tests in adults and children and of the histories of diabetic patients in the two age groups shows the increasing importance of obesity, endocrine disturbances, and degenerative changes, particularly arteriosclerosis, in the causation of disturbances in carbohydrate metabolism and in the development of diabetes, with advancing age.

Of this series of 500 juvenile diabetics, 364 were traced to the present time. Of these, 303, or 83.2 per cent are living, and sixty-one (16.7 per cent) are dead. Of the 303 living patients, 41.25 per cent have been followed for ten years or less since the onset of the diabetes, 43.23 per cent have been observed from ten to twenty years, and 15.51 per cent have had the disease more than twenty years.

Diabetic coma was the principal cause of death in this series, accounting for thirty-one of the sixty-one deaths. Only six of these thirty-one patients were under my immediate care at the time of death; of these six, one was treated in the preinsulin era and three were moribund and died within one hour after admission to the hospital. The others were under the care of their family physicians, mostly in small towns, at the time of the emergency. The second most important cause of death was intercapillary glomerulosclerosis, which brought death to eleven of the sixty-one patients. The other deaths occurred after infections, surgical operations, or accidents. Deaths in these sixty-one patients occurred from within less than a year to twenty-four years after onset of the diabetes. The largest number died within the first year, i. e., eighteen of the sixty-one (29.5 per cent). Thirty-seven of the deaths occurred in males and twenty-four in females.

As shown by the mortality figures, diabetic coma is the most serious complication threatening the child with diabetes. According to the records in this series, as experience has been gained by physicians and as the training of younger physicians in the handling of emergencies has improved, the incidence of diabetic coma has become considerably less than in the first decade after insulin was discovered. In this series, there were 218 patients seen from 1920 to 1934, and of these, fifty are known to have had diabetic coma (23 per cent). In the period 1934 to 1948, twenty-seven patients (9.5 per cent) had diabetic coma. Of the seventy-seven patients with this complication, fifty-four were under my personal care at the time of the emergency, with a total of six deaths. Twenty-three patients received treatment for the diabetic coma by their family physicians, and in this group there were eighteen deaths.

The optimism concerning the fate of diabetic children which represented the general consensus in the years immediately following the discovery of insulin has been modified considerably in recent years by the high incidence of premature arteriosclerotic changes in these patients, leading to retinopathy and glomerular changes in the kidney which have led to blindness and early death in many instances. In this series, eleven of the sixty-one deaths (18 per cent) were due to intercapillary glomerulosclerosis.

In a series of eighty-three patients in this series whom I have been able to observe by regular periodic examinations over a period of years, twenty-six (31.3 per cent) show albuminuria. In this series, the incidence of albuminuria is not significantly higher in patients who have had diabetes for ten to twenty-five years than in the group who have had the disease less than ten years. Other authors report an increasing incidence with longer duration of diabetes.

REFERENCES

1. Schwartzman, J., Crusins, M., and Beirne, D. P.: Diabetes Mellitus in Infants Under One Year of Age, *Am. J. Dis. Child.* 74: 587-606, 1947.
2. Priesel, R., and Wagner, R.: Studien über das Manifestationsalter und die Hereditätsverhältnisse des kindlichen Diabetes mellitus, *Msch. Kinderhik.* 44: 412, 1929.
3. Pirquet, C.: Quoted by Priesel u. Wagner, *Die Zuckerkrankheit und ihre Behandlung im Kindesalter*, Leipzig, 1932, Georg Thieme.
4. Joslin, E. P., and White, P.: Diabetes in Children, *J. PEDIAT.* 12: 255, 1938.
5. Saundby, Robt.: *Lectures on Renal and Urinary Diseases*, Bristol, 1896, John Wright & Sons, Ltd.
6. Friese, R., and Jahr, J. M.: Die Klinik des Diabetes mellitus in Kindesalter, *Abh. d. Kinderhik.* Berlin, 1932, S. Karger.
7. Toverud, K. U.: *Norsk. Mag. f. Laegevid* 88: 956, 1928.
8. Lion, G., and Moreau, C.: Diabète infantile familial, *Arch. d. méd. des Enfants* 12: 21-41, 1909.
9. Host, H. F.: Etiology and Cause of Diabetes Mellitus, *Norsk. Magsin f. Laegeev.* 8: 169-232, 1927.
10. Ladd, W. S.: Growth of Children with Diabetes Mellitus, *Am. J. Dis. Child.* 32: 812, 1926.
11. Collens, W. S., and Grayzel, H. G.: Management of Ambulatory Diabetic Child, *Am. J. Dis. Child.* 38: 275-293, 1929.
12. Smyth, F. S.: Analysis of Survey on Diabetic Children, *Calif. West. Med.* 25: 629-633, 1926.
13. John, H. J.: The Diabetic Child, Etiologic Factors, *Ann. Int. Med.* 8: 198-213, 1934.
14. Fischer, Alfred, E.: Personal communication.
15. Landabure, P. B., and Magdalena, A.: Las enfermedades infectiosas en la etiología de la diabetes infantil, *Dia Méd.* 10: 41, 1938.
16. Adams, S. F.: Seasonal Variations in Onset of Acute Diabetes, *Arch. Int. Med.* 37: 861-864, 1926.
17. Jones, A.: Referred to by von Noorden, *Die Zuckerkrankheit*, ed. 8, Berlin, 1927, Julius Springer.
18. Gilhespie, F. B., and Holden, H. S.: Grave Diabetes Mellitus with Pulmonary Tuberculosis Following Mumps, *Brit. M. J.* 2: 115, 1917.
19. Jacob, H. W.: Notes on a Case of Acute Pancreatitis Complicating Mumps, *British M. J.* 1: 1532, 1900.
20. Harris, H. F.: A Case of Diabetes Mellitus Quickly Following Mumps, *Boston M. & S. J.* 140: 465, 1899.
21. Lierle, D. M., and Potter, J. J.: Role of Chronic and of Subacute Infections in Diabetic Children, *Arch. Otolaryng.* 14: 432-439, 1931.
22. Wendt, L. F., and Peck, F. B.: Review of 1073 Cases of Diabetes Mellitus, *Am. J. Med. Sci.* 181: 52-65, 1931.
23. Lefkowitz, C. H.: Diabetic Purpura, *Arch. Pediat.* 23: 73, 1906.
24. Smith, R. P.: Diabetes in a Child Three Years of Age, *Canad. M. A. J.* 17: 214-216, 1927.
25. Sweeney, J. Shirley: Pancreatitis in Diabetes Mellitus, *Endocrinol.* 15: 508, 1931.
26. Brems, A.: Alimentary Hyperglycemia in Certain Infectious Disturbances, *Ugeskrift for Laeger* 94: 403, 1932.
27. Freund, H., and Marchand, F.: Ueber das Verhalten des Blutzuckers im Fieber, *Deutsch. Arch. f. klin. Med.* 110: 120-127, 1913.
28. Rau, H.: Diabetesbehandlung im Kindesalter, *Deut. med. Wehnschr.* 58: 171-173, 1932.
29. Hector, F. J.: Carbohydrate Metabolism in Diphtheria, *Lancet*, 2: 633, 1926.
30. Kasanin, J., Grabfield, G. P.: Blood Sugar Curves in Epidemic Encephalitis, *Arch. Int. Med.* 37: 102-109, 1926.
31. McCowan, P. K.: Blood Sugar Studies in Epidemic Encephalitis, *Lancet*, 1: 795-844, 1926.

32. Brugge, T., Dressel, K., and Lewy, G. H.: Beiträge zur Stoffwechselneurologie. *Ztschr. f. exp. Path. u. Ther.* 21: 358-379, 1920.
33. Aschner, B.: Zur Physiologie des Zwischenhirns, *Wien klin. Wochenschr.* 25: 1042, 1912.
34. Karplus, J. P., and Kreidl, A.: Gehirn und Sympathicus, *Pflüger's Arch. f. d. ges. Physiol.* Bonn 135: 406, 1910.
35. Nordmann, M.: Glykogenleber bei Poliomyelitis anterior, *Virehows Arch. f. path. Anat.* 263: 832-835, 1927.
36. Labbé, M., and Boulin, R.: Troubles de la glyco régulation au cours des infections, *Bull. et mem. Soc. Méd. d'hop. de Paris* 49: 1358-1368, 1925.
37. Lawrence, R. D.: Inhibition of Insulin Action by Toxemias, *British M. J.* 2: 983-984, 1926.
38. Fukuda, T., and Itabashi Ko: Hyperglycemia in Experimental Infection, *Ztschr. f. d. ges. exp. Med.* 76: 756, 1931.
39. Williams, J. L., and Dick, G. F.: Decreased Dextrose Tolerance in Acute Infectious Diseases, *Arch. Int. Med.* 1: 801-818, 1932.
40. John, H. J.: Glucose Tolerance Studies in Children and in Adolescents, *Endocrinology* 18: 75-85, 1934.
41. Anders, J. M., and Jameson, H. L.: Adiposity and Other Etiological Factors in Diabetes Mellitus, *Am. J. M. Sc.* 170: 313-324, 1925.
42. Mouriquand, G.: Obesity in Children, *Lyon méd.* 129: 883, 1920.
43. Zeek, Pearl: Juvenile Arteriosclerosis, *Arch. Path.* 10: 417-446, 1930.
44. White, P., and Waskow, E.: Arteriosclerosis in Childhood Diabetes, *Proc. Amer. Diab. Assn.* 8: 141-149, 1948.
45. John, H. J.: Ten Years Study and Follow Up of Cases of Hyperthyroidism Showing Carbohydrate Metabolism Disturbances, *J. A. M. A.* 99: 620-627, 1932.
46. John, H. J.: Diabetic Coma in Children, *Amer. J. Dig. Dis. & Nutr.* 1: 569-578, 1934.
47. Henderson, L. L., Sprague, R. G., Wagener, H. P.: Intercapillary Glomerulosclerosis, *Am. J. Med.* 3: 131-144, 1947.
48. Dolger, H.: A Clinical Evaluation of Vascular Damage in Diabetes Mellitus, *Proc. Amer. Diab. Assn.* 6: 397-405, 1946.

RENAL FUNCTION IN DIABETES INSIPIDUS

LEWIS BARTA, M.D.
BUDAPEST, HUNGARY

ALTHOUGH the rate of glomerular filtration is considerably influenced by endocrine factors,^{1, 2} the amount of glomerular filtrate is usually normal in diabetes insipidus.^{3, 4} Polyuria is a consequence of decreased tubular reabsorption. There are, however, cases in which the excretion of creatinine is considerably decreased.⁵ This could point to a decrease of the glomerular filtration rate.

In two patients suffering from diabetes insipidus, observations were made in order to investigate the connection of glomerular filtration rate and tubular reabsorption.

CASE REPORTS

CASE 1.—Sz. I., a male patient 8 years of age, had been suffering from diabetes insipidus for eight years, when it was observed that the amount of urine that had always amounted to from 3 to 4 L. a day decreased to from 650 to 850 ml. The specific gravity of the urine remained as low as 1001 to 1002 in spite of the fact that polydipsy had ceased. Analyses of the blood revealed 362 mg. per cent chlorine, 313 mg. per cent sodium, 20 per cent nonprotein nitrogen, 190 mg. per cent cholesterol, 1.6 mg. per cent creatinine, 21 mg. per cent urea; blood pressure was 90/45 mm. Hg. In the urine there were 394 mg. per cent chlorine, 179 mg. per cent urea, 20 mg. per cent creatinine. According to double glucose and galactose tolerance tests following administration of insulin and cortical extract, carbohydrate metabolism was normal. There was slight hypo-proteinemia with 3.9 Gm. of albumin and 1.9 Gm. of globulin per 100 ml. of blood. Urine creatinine per plasma creatinine was 12.5, diuresis per minute 0.5 ml., and the clearance of creatinine 6.25 ml. According to that value, the glomerular filtration rate was very low. Urinary output remained, however, normal owing to the tubular work characteristic of diabetes insipidus, i.e., urine amounted only to 8 per cent of the glomerular filtrate.

After administration of 6 gr. of sodium chloride to the patient weighing 28 kg., chlorine in the serum rose from 369 mg. per cent to 426 mg. per cent in ninety minutes. A rise of more than 35 mg. per cent is said to be characteristic of diabetes insipidus.⁶ In the urine the original chlorine level of 394 mg. per cent decreased to 117, 144, 167, and 171 mg. per cent. The phenomenon was followed by diuresis as 800 ml. of urine were excreted during the next three hours. In this period urine creatinine per plasma creatinine was 8.3, diuresis per minute 4.7 ml., and the amount of glomerular filtrate 39.01 ml. Diabetes thus became manifest. In consequence of the increased rediffusion of chlorine, excretion of minerals could not be increased only by increasing the volume of urine. In spite of the percentile decrease of urinary chlorine, the absolute quantity excreted of that mineral was considerably raised.

The patient was then given 5 mg. of desoxycorticosterone acetate intramuscularly every day for three days. During this period the daily amount of urine fell, in spite of the standard diet, from 600 ml. to 300 ml. Excretion of

minerals was also decreased; potassium in the urine decreased from 90 mg. per cent to 23 mg. per cent, sodium to 48 mg. per cent, chlorine to 85 mg. per cent, urea to 36 mg. per cent, and total nitrogen to 60 mg. per cent. In the plasma the following values were found: sodium 317 mg. per cent, potassium 16 mg. per cent, chlorine 390 mg. per cent, nonprotein nitrogen 20 mg. per cent. Urinary creatinine per plasma creatinine was 5.3 per 1.1 = 4.8, diuresis per minute 0.2 ml., glomerular filtrate 0.96 ml. The excretion of both urea and potassium suffered a considerable decrease following administration of desoxycorticosterone acetate. Following administration of posterior pituitary extract, the specific weight of urine rose to 1019; urinary creatinine per plasma creatinine was 88 per 1.3 = 67. After discontinuation of the extract, the specific weight of urine fell to the original value of 1001.

The latent stage of diabetes insipidus was observed for about three months; then the patient was discharged. According to a follow-up examination three months later he completely recovered from the condition. There has never been any indication of a renal lesion.

CASE 2.—Sz. K., a female patient 8 years of age, had been excreting 3 to 5 L. of urine a day for years. At admission, urinary creatinine per plasma creatinine was 10 per 0.8 = 12.5, diuresis per minute 2.4 ml., glomerular filtration rate 30 ml. The desoxycorticosterone acetate was administered intramuscularly in doses of 5 mg. a day for five days. Following this the output of urine rose to from 7 to 8 L. a day and a decrease occurred in the clearance of creatinine: $V_c/P_c = 2/0.6 = 3.3$. Before desoxycorticosterone acetate administration in the urine, there were potassium 40 mg. per cent, chlorine 196 mg. per cent, and total nitrogen 204 mg. per cent. After treatment the values were reduced to potassium 32 mg. per cent, chlorine 100 mg. per cent, and total nitrogen 80 mg. per cent. Chlorine in the serum was 400 mg. per cent before treatment and 410 mg. per cent after it. Posterior pituitary extract had a favorable effect; diuresis fell to 1 L. a day.

The clearance of inulin was also determined in this case. One hundred milliliters of a 10 per cent solution in saline was injected intravenously and an additional 100 ml. of the solution were infused in the next one-half hour. Blood and urine were collected every ten minutes and inulin, creatinine, and urea determined in every sample. Data are tabulated in Table I.

TABLE I

	PERIODS OF 10 MINUTES		
	1ST	2ND	3RD
Diuresis, ml./min	14.5	8.1	10.8
Inulin in urine	308	785	915
Inulin in plasma	145	157	149
V_c/P_c	2.1	5	6.1
Glomerular filtration rate, ml.	31	40.5	66
Creatinine in urine	-	5	6
Creatinine in plasma	-	0.8	0.8
V_c/P_c	-	6.2	7.5
Urea in urine	-	58	55
Urea in plasma	-	17	17
V_u/P_u	-	3.4	3.2

The diuresis following administration of inulin is partly connected with sodium chloride, partly with the effect substances of a high molecular weight exert on osmo-regulation. Patients suffering from diabetes insipidus are sensitive to similar stimuli as was well illustrated by the changes in the rate of glomerular filtration. There was little difference between the clearance rates

of inulin and creatinine, the higher values for the latter substance might be ascribed to tubular excretion. The low urea values are due to tubular reabsorption. There was little divergence between the amounts of urine excreted during the three periods in spite of the fact that the rate of glomerular filtration rose to twice the original value. This shows that the rate of tubular reabsorption increased parallel with the glomerular filtration rate.

The origin of the condition could not be cleared either from the history or by examination. There was no indication whatever of a renal lesion.

COMMENT

The first patient recovered from diabetes insipidus at the onset of puberty. Prior to this, the condition that had been manifest for many years became latent. The amount of urine was normal in this period but its specific weight remained as low as 1001 to 1002 and the excretion of both minerals and nitrogen was also low. The latter phenomenon can be partly ascribed to the fact that 5 kg. of weight was put on during the latent period. The glomerular filtration rate was very low but tubular reabsorption of water corresponded to a state of diabetes insipidus and the amount of urine excreted remained normal. The condition could be well influenced by posterior pituitary extract. Both the rate of glomerular filtration and reabsorption in the tubular system could be normalized by that substance. Nephrogenic diabetes insipidus⁷ could, therefore, be excluded. The fact that there was an increase in the glomerular filtration rate following administration of sodium chloride speaks also against renal lesion. Following desoxycorticosterone acetate there was a further decrease in the glomerular filtration rate and also in the excretion of potassium, sodium, chlorine, and nitrogen, and in the tubular reabsorption of water which amounted to 80 per cent of the glomerular filtrate.

The second case could also be influenced by posterior pituitary. Polyuria was augmented by desoxycorticosterone acetate, which caused a moderate decrease of the glomerular filtration rate and a considerable reduction of tubular reabsorption. Urinary creatinine fell to 2 mg. per cent. A rediffusion of 80 per cent of the glomerular filtrate is an obligatory process⁸ and as only 20 per cent of it is under neurohormonal influence, it had to be supposed that some tubular lesion due to creatinine was the cause of the passive rediffusion of the substance.⁹ The supposition was not confirmed by the clearance rate of inulin as in the first period this was 2.1 with a diuresis of 14.5 ml. per minute, i.e., nearly 50 per cent of the glomerular filtrate was reabsorbed. Tubular reabsorption of 80 per cent of the glomerular filtrate may be obligatory under normal conditions but, according to the inulin clearance rate, the values obtained for creatinine have to be regarded as real in the present case.

The considerable diuresis observed following administration of inulin may have been due partly to the sodium chloride injected. In this period there was a considerable increase of glomerular filtration and tubular reabsorption. In Case 2, there was, therefore, no change in the minute rate of diuresis. The effect of sodium chloride is contrary to that of desoxycorticosterone acetate following administration of which substance both glomerular filtration rate and tubular reabsorption were reduced.

According to the above, the glomerular filtration rate plays a significant role in the water and salt metabolism of patients suffering from diabetes insipidus. In Case 1, a spontaneous reduction of the glomerular filtrate occurred during the period preceding recovery and at the same time the amount of water reabsorbed in the tubules was also decreased together with the excretion of minerals and nitrogen. Desoxycorticosterone acetate increased the retention of salts and nitrogen and reduced the rate of glomerular filtration. In Case 2, the glomerular filtrate was only moderately reduced by desoxycorticosterone acetate with a parallel increase in the excretion of potassium and a decrease in the excretion of other minerals and nitrogen. In this case the tubular reabsorption of water was reduced to such a degree that a considerable increase of polyuria occurred and the condition of the patient was aggravated. It must be noted that in infants and small children, in which increase in weight owing to water and salt retention was achieved by desoxycorticosterone acetate, there was always a decrease in the clearance of creatinine. In cachectic patients desoxycorticosterone acetate often caused loss of weight and marked polyuria.^{9, 10}

According to our observation, decrease in glomerular filtration rate was followed by reduction of tubular reabsorption. The changes were not wholly parallel. In Case 1, the reduction of glomerular filtrate following administration of desoxycorticosterone acetate was more significant than that of tubular reabsorption, consequently oliguria resulted. In Case 2, the decrease of the glomerular filtration rate remained insignificant while a considerable reduction occurred in the rate of tubular reabsorption, thus polyuria appeared. It is probable that the effect desoxycorticosterone acetate exerted on the renal function of both patients was in connection with the changes in water- and salt-retaining capacity of the tissues.

SUMMARY

According to observations made on two patients suffering from diabetes insipidus, it is probable that the changes in glomerular filtration rate play a significant role in the regulation of water and mineral metabolism in diabetes insipidus. In Case 1 polyuria was controlled by a decrease in glomerular filtration and at the same time water and salt retention was increased. In this period the condition could be made manifest by administration of sodium chloride. In both cases glomerular filtration and tubular reabsorption were both decreased by desoxycorticosterone acetate. The rate of reduction of the two functions were, however, in no relation with one another so that polyuria appeared in the first case and oliguria in the second one. The effect of desoxycorticosterone acetate on renal function is probably in connection with its influence on the salt and water retention of the tissues.

REFERENCES

1. Hare, Donald, Bradshaw, Chambers, and Hare: Am. J. Dis. Child. 69: 257, 1945; Am. J. Physiol. 141: 187, 1944.
2. Margittay, Becht, and Gömöry: Die Nierenfunktion bei der Addisonischen Krankheit, Ztschr. f. exper. Med. 104: 22, 1939.

3. Popper and Mandel: Filtrations und Resorptionsleistung in der Nierenpathologie, Ergebni. d. inn. Med. u. Kinderh. 53: 685, 1937.
4. Bansi: Zur funktionellen Pathologie des Diabetes insipidus, Ztschr. f. d. ges. exper. Med. 111: 501, 1942.
5. Caccuri: Neurohypophysis Zustandsbilder, Kongressblatt inn. Med. 79: 452, 1935.
6. Lippmann: Der Kochsalzbelastungsversuch in der Pädiatrie und seine klinische Bedeutung, Ann. paediat. 161: 57, 1943; and 161: 145, 1943.
7. Williams and Henry: Nephrogenic Diabetes Insipidus Transmitted by Females and Appearing During Infancy in Males. Ann. Int. Med. 27: 84, 1947.
8. Rusznyák: Az egészséges és beteg vese működése. Orvosi hetil 89: 321, 1948.
9. Barta: Oliguriás diabetes insipidus az endogen kreatinin clearance jelentős csökkenésével. Orvosi hetil. 90: 270, 1949.
10. Barta: Influence of Desoxycorticosterone Acetate on the Clearance of Creatinine, Paed. Danub. 5: 137, 1949.

THE EFFECT OF ANTIHISTAMINIC DRUGS ON THE TUBERCULIN PATCH TEST

EDWIN L. KENDIG, JR., M.D., WILLIAM P. SPENCER, M.D., AND
CARL W. LAFRATTA, M.D.
RICHMOND, VA.

THE tuberculin test is an important diagnostic aid in all tuberculosis, but it is of particular value in tuberculosis of childhood. Any drug which might conceivably interfere with this test by causing a "false negative" reaction should be investigated. Since the antihistaminic drugs have been shown to inhibit urticarial response in many dermatoses,^{1, 2, 3} and since use of these drugs has become widespread, the present study was undertaken.

THE STUDY

On a group of twenty patients at the Pine Camp Hospital a tuberculin patch test (Vollmer) was performed. After forty-eight hours the patch was removed and forty-eight hours later the test was read. All the tests were positive, but to a varying degree.

Eight hours before the second patch test was applied an antihistaminic drug was instituted by mouth. Eleven patients were given Antistine in dosage of 150 mg. for the first day and 300 mg. daily for the ensuing four days until the test was read. Eight patients were given Pyribenzamine in the same dosage, and one had Pyribenzamine 150 mg. daily for the five-day period.

RESULTS

In that group taking Antistine, the degree of tuberculin reaction was actually slightly greater in 5 instances, and in no case was less marked (see Table I). Among those taking Pyribenzamine, the degree of tuberculin reaction was slightly greater in one case and slightly less in two instances (see Table I). In none of the above cases was the difference great, and in all others there was no difference in the tuberculin reaction with and without antihistaminic drug administration. All readings were done by the same individuals in order to insure uniformity of interpretation.

TABLE I. TUBERCULIN REACTION AFTER ANTIHISTAMINIC DRUGS

DRUG	PATIENTS	MORE REACTION	LESS REACTION
Antistine	11	5	0
Pyribenzamine	9	1	2
Totals	20	6	2

The Antistine and Pyribenzamine were supplied through the generosity of Ciba Pharmaceutical Products, Summit, N. J.

The tuberculin patch tests were made available through the courtesy of the Lederle Laboratories, Pearl River, N. Y.

DISCUSSION

The value of the routine tuberculin test as an aid in diagnosis of tuberculosis is well recognized. In order to avoid an extra needle puncture, many physicians, particularly those treating children, employ the tuberculin patch test (Vollmer) in this manner. The pertinent question is whether or not ingestion of an antihistaminic drug at the time of the application of the tuberculin test can inhibit a positive reaction in an individual with tuberculous infection. In our study the antihistaminic drugs had no inhibitory effect on the reaction of the tuberculin patch test.

Boquet,⁴ in guinea pig experiments with the earlier antihistaminic drugs, found that the tuberculin reaction was unchanged. In more recent studies Guy⁵ and Criepp⁶ and associates found the antihistaminic drugs to be without inhibitory effect on the intradermal tuberculin test, and the latter also showed that intradermal Pyribenzamine and Pyribenzamine by iontophoresis had no effect on the reaction of the tuberculin patch test. Sarber,⁷ working with guinea pigs, found that Benadryl gave a reduction in the tuberculin skin reaction, and felt that other investigators had failed to arrive at this conclusion because they had not used threshold doses.

The present study was conducted only to determine whether or not ingestion of the antihistaminic drugs inhibited the tuberculin patch test, a case finding technique widely used in pediatrics. No inhibition was noted.

SUMMARY

In a study of twenty tuberculous individuals, administration of Antistine and Pyribenzamine by mouth produced no change in the skin reaction of the tuberculin patch test.

We appreciate very much the help of those patients and members of the staff of Pine Camp Hospital whose cooperation made this study possible.

REFERENCES

1. Feinberg, S. M.: Histamine and Antihistaminic Agents: Their Experimental and Therapeutic Status, *J. A. M. A.* 132: 703, 1946.
2. Lynch, F. W.: Benadryl in Dermatologic Therapy, *Arch. Derm. and Syph.* 55: 101, 1947.
3. Mayer, R. L.: Pyribenzamine in Experimental Nonallergic and Allergic Dermatitis, *J. Invest. Derm.* 8: 67, 1947.
4. Boquet, A.: Substances Antihistaminiques et Reaction Tuberculiniques, *Annales de l'Inst. Pasteur* 69: 55, 1943.
5. Guy, W. B.: The Effect of Pyribenzamine on the Tuberculin Reaction in Man, *J. Invest. Derm.* 8: 335, 1947.
6. Criepp, L. H., Levine, M. I., and Aaron, T. H.: Inhibition of Tuberculin Type Reaction by Antihistaminic Drugs and Rutin, *Am. Rev. Tuberc.* 59: 701, 1949.
7. Sarber, R. W.: Effect of Benadryl Hydrochloride on the Tuberculin Reaction in Guinea Pigs, *Am. Rev. Tuberc.* 57: 504, 1948.

THE BETA DISTURBANCE OF THE ELECTROPHORETIC PATTERN OF BLOOD SERUM IN POLIOMYELITIS

V. C. KELLEY, PH.D., M.D.,^{*} DORIS DOEDEN, M.S., T. N. HALL, M.D.,
AND I. MCQUARRIE, PH.D., M.D.
MINNEAPOLIS, MINN.

IN electrophoretic patterns of blood serum obtained by the Longsworth "schlieren scanning" technique¹ there is commonly observed in the beta globulin region of the descending boundary a disturbance which appears as a sharp spike extending indefinitely out of the picture. In a preliminary study of the electrophoretic characteristics of the blood serum in poliomyelitis reported from this laboratory,² it was observed that definite abnormalities in this beta disturbance commonly occurred in the patterns obtained in that disease.

Two recent epidemics of poliomyelitis in Minnesota have made it possible for us to obtain blood serum from a large number of individuals afflicted with this disease. Using this material we have now completed a more extensive study in an attempt to evaluate the significance of our preliminary observation of the occurrence of abnormalities in the beta disturbance of the electrophoretic patterns of blood serums obtained from cases of poliomyelitis.

MATERIALS AND METHODS

The blood specimens in the cases of poliomyelitis were obtained, with a few exceptions, from patients in the Department of Pediatrics of the University of Minnesota Hospitals. The normal control subjects were selected from visitors to a large pediatric out-patient clinic and included children who came to the clinic for psychiatric evaluation, dental examination, eye examination, or minor congenital anomalies. These children were all free of recent or existing disease as determined by histories and routine physical and laboratory examinations. All blood specimens drawn were morning, fasting specimens.

The serum was separated at once and stored at -30° C. until used. Before being submitted to electrophoresis, each sample was diluted with three volumes of a phosphate buffer of pH 7.8 and ionic strength of 0.1 or a veronal buffer of pH 8.65 and ionic strength of 0.1 and was then dialyzed against a large volume of the same buffer for three days.

The electrophoretic patterns of these diluted serums were then obtained after 120 minutes of electrophoresis under a potential gradient of 5.33 volts per centimeter by the "schlieren scanning" method of Longsworth.¹

EXPERIMENTAL

In the present report, as in our previous report,² the changes in the beta disturbance are classified as 0 to 3+, where 0 is taken to mean no change in the

^{*}From the Department of Pediatrics, University of Minnesota.

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*Swift Foundation Nutrition Fellow.

beta disturbance (i.e., it appears as a narrow, tall peak) and 3+ is taken to mean the complete absence of the beta disturbance. 1+ indicates a definite shortening and broadening of the beta disturbance, and 2+ indicates a very marked decrease of the beta disturbance but not its complete absence. Fig. 1 shows typical electrophoretic patterns illustrating these various degrees of beta disturbance.

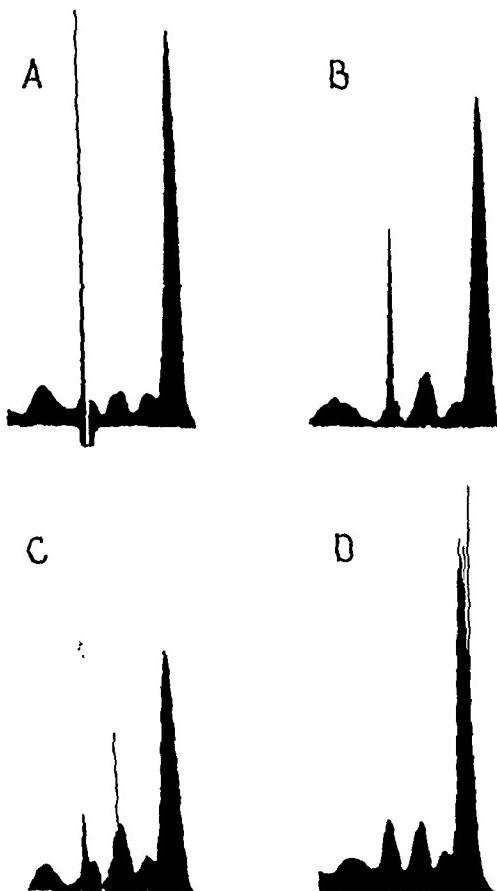


Fig. 1.—Three degrees of alteration in the beta disturbance of the electrophoretic pattern (descending boundary). A shows the beta disturbance appearing as a narrow spike of infinite length (0 change); B represents 1+ change; C, 2+ change; and D, 3+ change (complete absence of beta disturbance).

A total of 252 electrophoretic experiments are included in this report. Of these, 212 are on serum samples from poliomyelitis patients, 142 done in veronal buffer at pH 8.65, and 70 in phosphate buffer at pH 7.8. The remainder are on serum samples from normal children, 20 done in each of these buffers.

The results of the electrophoretic studies done on serum samples from poliomyelitis patients are summarized in Table I. From this table it may be seen that in veronal buffer 50 per cent of the patterns showed a marked change

or absence of the beta disturbance, that is, 2+ or 3+ change, while in phosphate buffer 78.5 per cent of the patterns showed such major changes. These data are in agreement with those of our previous study² in that in the phosphate buffer only two patterns (2.9 per cent of the cases) showed 0 change, the other 97.1 per cent of the cases showing at least a 1+ change. The hospital charts of all of these patients were carefully analyzed in an attempt to correlate the occurrence of changes in the beta disturbance with varying clinical manifestations of the disease. No correlation was found to exist between the appearance of the beta disturbance and the age or sex of the patient, the extent of paralysis, the occurrence of bulbar symptoms, or the temperature and pulse of the patient at the time the blood sample was obtained. There is likewise but little correlation of the appearance of the beta disturbance with the duration of the disease. As shown in Table I major changes in the beta disturbance occurred more frequently in the first ten days after the onset of the disease than later in patterns done in phosphate buffer but the reverse was true in patterns done in veronal buffer.

TABLE I. THE BETA DISTURBANCE IN SERUM SAMPLES FROM POLIOMYELITIS PATIENTS

BUFFER	TIME AFTER ONSET	NUM- BER OF SAM- PLES	NO CHANGE		1+ CHANGE		2+ CHANGE		3+ CHANGE		PER CENT SHOWING NO OR SLIGHT CHANGE	PER CENT SHOWING MARKED CHANGE	
			NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT			
Veronal	1-10 days	77	21	27.3	21	27.3	17	22.1	18	23.3	54.6	45.4	
	More than 10 days	65	11	16.9	18	27.7	13	20.0	23	35.4	44.6	55.4	
Phos- phate	Total	142	32	22.5	39	27.5	30	21.1	41	28.9	50.0	50.0	
	1-10 days	41	1	2.4	6	14.6	9	22.0	25	61.0	17.0	83.0	
	More than 10 days	29	1	3.4	7	24.1	10	34.5	11	38.0	27.5	72.5	
			Total	70	2	2.9	13	18.6	19	27.1	36	51.4	21.5

During the progress of these studies, it became apparent that there was a definite difference in the incidence of major changes in beta disturbance occurring in phosphate buffer as compared to veronal buffer. For this reason, a series of forty cases was subjected to parallel studies in the two buffers. In these cases the serum obtained from a particular blood sample from a poliomyelitis patient was divided into two portions, one portion being studied in veronal buffer, the other in phosphate. The results of these studies are shown in Table II. The data obtained verified our original impression that there was a much greater incidence of major abnormalities in the beta disturbance of electrophoretic patterns obtained in phosphate buffer than of patterns obtained in veronal buffer. Analysis of the data presented in Table II reveals that a 3+ change in beta disturbance occurred in twenty-five of forty cases (62.5 per cent) in phosphate buffer as compared to only eight of forty cases (20 per cent) in veronal buffer. Also of the same forty cases, ten (25 per cent) showed a 0 change in beta disturbance in veronal buffer but none showed a 0 change in phosphate buffer. In only three cases was the change in beta disturbance greater in veronal than in phosphate buffer, while in twenty-five

TABLE II. INFLUENCE OF BUFFER ON OCCURRENCE OF CHANGE IN BETA DISTURBANCE

PATIENT	CHANGE IN BETA DISTURBANCE		PATIENT	CHANGE IN BETA DISTURBANCE		PATIENT	CHANGE IN BETA DISTURBANCE	
	PHOSPHATE	VERONAL		PHOSPHATE	VERONAL		PHOSPHATE	VERONAL
R. H.	2+	2+	G. B.	3+	3+	R. F.	3+	3+
R. W.	1+	0	A. K.	2+	0	M. N.	3+	1+
L. S.	1+	2+	E. C.	2+	2+	S. A.	3+	2+
J. S.	1+	0	J. S.	3+	2+	J. B.	2+	2+
K. B.	3+	1+	R. W.	3+	3+	A. B.	2+	1+
J. L.	2+	2+	G. S.	3+	2+	R. S.	3+	1+
T. W.	2+	0	R. B.	3+	0	A. E.	3+	1+
W. W.	2+	0	B. M.	1+	0	E. J.	3+	1+
J. G.	3+	3+	M. H.	3+	2+	H. R.	3+	1+
H. E.	2+	2+	W. F.	3+	3+	E. D.	3+	1+
S. M.	3+	0	G. B.	2+	3+	J. H.	3+	0
R. S.	3+	0	J. E.	3+	3+	L. R.	1+	2+
W. M.	3+	2+	J. L.	3+	1+			
T. N.	3+	3+	P. C.	3+	1+			

cases it was greater in phosphate than in veronal. In veronal buffer 50 per cent of these forty cases showed a major change in beta disturbance (2+ or 3+ change), while in phosphate buffer 87.5 per cent showed a similar change. These figures are in good agreement with the data obtained in the larger series which are shown in Table I.

In order to ascertain whether or not results such as those obtained with poliomyelitis serums (Table I) represented significant deviations from the normal, a series of serum samples from normal children was studied electrophoretically in both phosphate and veronal buffers. Table III shows the results of these studies. It is apparent from these data that in the case of serums from normal subjects, as well as in the case of serums from subjects with poliomyelitis, the type of buffer used influences profoundly the appearance of the beta disturbance of the electrophoretic pattern. It is also apparent that the beta disturbance of normal serum is not necessarily a tall, narrow, spike but that it may vary over the entire range from such an appearance to complete absence. There does appear to be, however, a difference in incidence of occurrence of major changes in the beta disturbance between electrophoretic patterns of normal serum and of serum of poliomyelitis patients. Whereas in normal serums only 20 per cent of the patterns done in veronal buffer and 65 per cent of the patterns done in phosphate buffer show 2+ or 3+ changes in the beta disturbance, in poliomyelitis serums 50 per cent of the patterns done in veronal buffer and 78.5 per cent of the patterns done in phosphate buffer show similar changes. Statistical evaluation of these data

TABLE III. THE BETA DISTURBANCE IN SERUM SAMPLES FROM NORMAL CHILDREN

BUFFER	NUMBER OF SAMPLES	NO CHANGE		1+ CHANGE		2+ CHANGE		3+ CHANGE		PER CENT SHOWING NO OR SLIGHT CHANGE	PER CENT SHOWING MAJOR CHANGE
		NO.	PER CENT								
Veronal	20	9	45	7	35	2	10	2	10	80	20
Phosphate	20	5	25	2	10	5	25	8	40	35	65

reveals that the differences observed in veronal buffer between normal serums and poliomyelitis serums are statistically significant, while those observed in phosphate buffer are not. However, it appears very likely that if the series were sufficiently expanded these consistent differences would also become statistically significant.

DISCUSSION

The exact cause of the beta disturbance still remains unknown. It was considered by Longsworth and co-workers^{3, 4} to be due to convections arising from reactions in the neighborhood of the beta boundary following the electrophoretic separation of the components. In the process of electrophoretic separation there results a situation in which in the descending leg of the electrophoresis cell the beta globulin is migrating in the absence of albumin and alpha globulin, whereas in the ascending leg of the cell it is not. Longsworth and his collaborators suggest that the absence of the albumin and alpha globulin fractions in the beta region in the descending leg of the electrophoresis cell may result in a stability change which permits the convections of which they speak to arise, thus explaining the appearance of a beta disturbance in the descending but not in the ascending electrophoretic pattern.

It has been postulated⁵ that this beta disturbance spike, extending indefinitely out of the picture of the descending boundary, corresponds to the presence of a turbidity and that the disturbance is not entirely dependent on a refraction gradient. The turbid material transmits no light and, therefore, the spike is of infinite length. However, the dense layer is not too opaque to transmit light in all cases; in cases in which light is transmitted the spike does not have infinite length, but the pattern simply shows a steep gradient at that point.

There has been considerable difference of opinion concerning the origin of this turbidity. The suggestion has been made⁵ that it might be due to an interaction between alpha and gamma globulin. According to Longsworth and his collaborators³ it may be due to a stability change by removal of other components. Moore points out, however, that, if this were true, it would appear that the entire beta region which is free of albumin and alpha globulin should show turbidity rather than just the narrow region near the slow end of the beta boundary. Abramson, Moyer, and Gorin⁵ suggest that there might be two beta globulins of different stabilities, the slower-moving one being more unstable in the absence of the faster-moving one.

Evidence supporting this latter view was brought forward by Chargaff, Ziff, and Moore⁶ who demonstrated that the addition of heparin causes disappearance of the beta disturbance. Chargaff⁷ suggests that the turbidity is associated with a weak lipoprotein complex existing in the components of the beta globulins which becomes partially dissociated when the beta components are under the influence of an electric field in the absence of the albumin and alpha globulin components of the serum, the situation which exists in the descending leg of the electrophoresis cell.

In agreement with this suggestion there is considerable evidence that the lipids of blood serum are present in the form of lipoprotein complexes of varying degrees of stability. Sørensen⁸ first suggested the occurrence of lipoprotein complexes in normal serum because he felt that the perfect clearness of such liquids as serum and plasma in spite of their contents of lipid materials could be explained only by assuming linkage between lipids and proteins. Tiselius^{9, 10} noted that most of the lipid material of normal serum and the opalescence of normal serum, due presumably to suspended fat globules, migrate with the beta globulin fraction. Abramson¹¹ has demonstrated that the mobility of a particle suspended in a protein solution is due to the adsorption of a layer of protein on the surface of the particle and, in general, has the same value as the mobility of the adsorbed protein. Therefore, it seems logical to conclude, as Longsworth⁴ has, that the suspended fat particles of serum are coated with a layer of beta globulin.

In electrophoretically separated serum proteins, lipids are present in all fractions with the largest amounts being associated with the beta globulin and alpha globulin fractions, respectively.¹² Kendall¹³ demonstrated that even four-times recrystallized human serum albumin contains a certain lipid residuum. Longsworth and MacInnes,⁴ working with nephrotic serum, found that high speed centrifugation cleared the serum by removal of fat particles but that cold ether extraction removed still more lipid material as evidenced by significant decreases in the beta globulin fraction. On the other hand, in the case of normal serum little lipid can be extracted by shaking with cold ether but considerably larger amounts can be removed by freezing in the presence of ether.¹⁴ Blix¹⁵ by extracting with cold acetone and Zeldis, Alling, McCoord, and Kulka¹⁶ by extracting with cold alcohol have succeeded in removing the major portion of the cholesterol and a large portion of the phospholipids from the serum proteins. However, Zeldis and his collaborators conclude in agreement with the finding of Kendall¹³ that a certain portion of the bound lipids can be freed only by denaturation of their protein components.

It is interesting to note that Zeldis and his collaborators¹⁶ observed regular disappearance of the beta disturbance in samples of serum extracted by cold alcohol whereas Longsworth and MacInnes⁴ found persistence of the beta disturbance following extraction with cold ether. This would appear to support the suggestion of Chargaff⁷ that the turbidity corresponding to the beta disturbance results from dissociation of a lipoprotein complex when the beta components are under the influence of an electric field in the absence of albumin and alpha globulin. In this connection it should also be noted that the beta disturbance is absent in electrophoretic patterns of nephrotic urine⁴ and of spinal fluid.¹⁷ In both of these cases it might be assumed that this lipoprotein complex, representing an entity of large particle size, is selectively removed by the membranes through which these fluids are filtered. Certainly one may say in these cases as well as in the cases of those samples of serum which have patterns with completely absent beta disturbance either that one of the constituents of the complex is missing or that conditions which favor formation of a turbid layer are absent.

Regardless of the exact mechanism involved, it is apparent from our data that in electrophoretic patterns done in phosphate buffer the occurrence of the beta disturbance as a narrow spike of infinite length is much less common and the complete absence of the beta disturbance is much more common than in patterns done in veronal buffer. Longsworth, Shedlovsky, and MacInnes³ reported that the beta disturbance is almost always observed in the pattern of the descending boundaries. Dole¹⁸ found that fourteen of fifteen normal subjects showed a beta disturbance and the fifteenth showed it on repetition. Furthermore, one subject showed the beta disturbance on nineteen of twenty runs, the one exception being when the blood was not drawn as a fasting sample. In our series of twenty normal children reported here, the beta disturbance is completely absent (3+ change) in 10 per cent of the patterns done in veronal buffer and in 40 per cent of the patterns done in phosphate buffer. It is present as a narrow spike of infinite length (0 change) in 45 per cent of the patterns done in veronal and in only 25 per cent of the patterns done in phosphate buffer.

Thus, it seems apparent that for some obscure reason there is less tendency to form a turbid layer in the beta component of the descending limb of the electrophoresis cell in the presence of phosphate buffer than in the presence of veronal buffer. If one accepts Chargaff's explanation of the beta disturbance, it may then be concluded that the dissociation tendency of the lipoprotein complex whose dissociation produces the turbidity corresponding to the beta disturbance is decreased in phosphate buffer as compared to its dissociation tendency in veronal buffer.

The greater incidence of occurrence of major changes in the beta disturbance in electrophoretic patterns of serum from poliomyelitis patients than in patterns of serum from normal subjects, irrespective of the buffer used, is a definite observation of our present study. In the previous paper² it was tentatively suggested that the dissociation tendency of the lipoprotein complex, whose dissociation produces the turbidity corresponding to the beta disturbance, is decreased in patients with poliomyelitis. An alternative explanation which should be considered is that this lipoprotein complex is absent or decreased in concentration in the serum of poliomyelitis patients. Perhaps careful investigation of the lipid constituents of such serums would yield important information in this regard. Until the true nature of the beta disturbance is more clearly understood, no definite conclusions as to the true significance of the changes which occur in patients with poliomyelitis are justified.

SUMMARY AND CONCLUSIONS

1. The patterns obtained in 252 electrophoretic experiments on blood serums of normal children and of poliomyelitis patients have been analyzed with regard to the appearance of the beta disturbance.
2. Marked changes (2+ and 3+ changes) in the beta disturbance were found to occur in the electrophoretic patterns of the serum of normal chil-

dren in 20 per cent of the cases done in veronal buffer and in 65 per cent of the cases done in phosphate buffer.

3. In cases of poliomyelitis similar changes were found to occur in 50 per cent of 142 cases that were studied in veronal buffer and in 78.5 per cent of 70 cases studies in phosphate buffer.

4. No correlation was found to exist between the changes observed in the beta disturbance and the severity or the duration of the disease.

REFERENCES

1. Longsworth, L. G.: J. Am. Chem. Soc. 61: 529, 1939.
2. Kelley, V. C., Briggs, D. R., and Jensen, R. A.: J. PEDIAT. 29: 433, 1946.
3. Longsworth, L. G., Shedlovsky, T., and MacInnes, D. A.: J. Exper. Med. 70: 399, 1939.
4. Longsworth, L. G., and MacInnes, D. A.: J. Exper. Med. 71: 77, 1940.
5. Abramson, H. A., Moyer, L. S., and Gorin, M. H.: Electrophoresis of Proteins, New York, 1942, Reinhold Publishing Corporation, p. 185ff.
6. Chargaff, E., Ziff, M., and Moore, D. H.: J. Biol. Chem. 139: 383, 1941.
7. Chargaff, E.: Lipoproteins, in Edsall, J. T., and Anson, M. L.: Advances in Protein Chemistry, New York, 1944, Academic Press, vol. I, p. 1.
8. Sørensen, S. P. L.: Compt. rend. d. trav. du lab. Carlsberg 18: 104, 1931.
9. Tiselius, A.: Kolloid Ztschr. 85: 129, 1938.
10. Tiselius, A.: Biochem. J. 31: 1464, 1937.
11. Abramson, H. A.: Electrokinetic Phenomena, The Chemical Catalog Co., New York, 1934, p. 147.
12. Blix, G., Tiselius, A., and Svensson, H.: J. Biol. Chem. 137: 485, 1941.
13. Kendall, F. E.: J. Biol. Chem. 138: 97, 1941.
14. McFarlane, A. S.: Nature 149: 439, 1942.
15. Blix, G.: J. Biol. Chem. 137: 495, 1941.
16. Zeldis, L. J., Alling, E. L., McCoord, A. B., and Kulka, J. P.: J. Exper. Med. 82: 411, 1945.
17. Kabot, E. A., Landow, H., and Moore, D. H.: Proc. Soc. Exper. Biol. & Med. 49: 260, 1942.
18. Dole, V. P.: Personal communication quoted in reference.²

MYOTONIA CONGENITA

DONALD R. HIRSCH, M.D., JOSEPH DANCIS, M.D., AND RICHARD S. WARD, M.D.
NEW YORK, N. Y.

MYOTONIA congenita is a hereditary condition in which the patient is unable to relax his muscles quickly after a strong voluntary contraction. It is commonly associated with muscular hypertrophy. The condition is usually not disabling and the prognosis for life is good. The disease is rare, but is one of great interest to physiologists because of the possibility that an understanding of the mechanisms behind the muscular abnormality will give us an insight into the physiology of normal muscular contraction.

Myotonia congenita was first described by Bell in 1833. It received general recognition, however, only after Thomsen described twenty-one cases in his own family in 1876. A related disease, dystrophia myotonica, is more common. This latter condition has an onset later in life and there are associated findings: muscular atrophy and weakness, cataracts, testicular atrophy, baldness, and a low basal metabolic rate. Most of the studies on myotonia have been carried out on patients with dystrophia myotonica, but so far as we know the muscular abnormality is the same in the two diseases, varying in severity. There are several good reports and reviews on this subject in the literature.^{1-6, 9, 10}

The justification for an additional report lies in the use of two new approaches to the study of myotonia: (1) a search for a humoral substance in the blood of a patient with myotonia, which would be capable of reproducing myotonia, and (2) observation of the effects of curare on the myotonic reaction. The latter of these techniques has become available for clinical research only in the past few years.

CASE REPORT

II. C., a 6-year-old Negro boy (B. H. 28255-47) was admitted to Bellevue Hospital in June, 1947, with a chief complaint of persistent symmetrical swellings in the neck region. It was also reported that the child seemed slow and lethargic in play.

The child came from a boarding school, and only the father was available to give a history. He described the patient's birth and neonatal development as normal, except perhaps for the fact that the child's muscular development had always seemed advanced for his age. Aside from measles, chicken pox, and appendicitis requiring operation, there had been no illnesses. The child had entered the boarding school eight months before the hospital admission and the admitting physician had noted the bilateral neck swellings, which he attributed to cervical lymphadenitis secondary to chronic tonsillitis. In the school, it was noted that the boy walked slowly and seemed sluggish in play, compared to the other children. He was also seen to have a peculiar staring mannerism, most noticeable in the early morning on awakening.

From the Department of Pediatrics, New York University-Bellevue Medical Center and the Children's Medical Service, Bellevue Hospital.

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The father and two brothers of the patient were healthy and free from muscular abnormalities. Both the mother and the maternal grandmother, however, were said to show prominent overdevelopment of the muscles of the neck and shoulder girdle, and to suffer from an inability to move rapidly. The mother had the same staring mannerism as the child.

Physical examination on admission showed an alert, intelligent, well-developed and well-nourished Negro boy of 6 years of age. He was not ill. Positive findings were limited to the skeletal muscle system and the eyes. The tonsils were large and cryptic, but free of active infection. There were no signs of hypothyroidism. Neurologic examination was negative except for the muscle findings.



Fig. 1



Fig. 2

Fig. 1—Obvious lid lag due to increased tonus of the levator palpebrae.

Fig. 2—The patient has been instructed to close his eyes tightly, and then open them as rapidly as possible. The photograph was taken about two seconds after the patient began to open his eyes. The palpebral orifice is still reduced in all diameters despite the maximal effort he is making to open his eyes.

The child's herculean build was striking. The masses in the neck region could be demonstrated to be hypertrophied sternocleido mastoid muscle rather than lymph nodes. The muscles of the shoulder girdle stood out clearly.

The abnormalities in eye movements first suggested to us that the patient was suffering from a generalized muscle disturbance. There was severe myotonia of all the extraocular muscles. The child had great difficulty in following rapidly moving objects with his eyes. If an object were moved vertically or horizontally in front of him, there would be a short interval before he could make his eyes move in the required direction. When he closed his eyes tightly and then tried to open them again, he could not do so for

several seconds, even though he tried hard. He had pronounced lid lag, which we attributed to myotonia of the levator palpebrae superioris. There was no exophthalmos.

These abnormalities of the extraocular muscles were most marked in the early morning on awakening. The myotonia disappeared rapidly when the affected muscles were "warmed up." Thus after the child had opened and closed his eyes several times in succession, the movements became progressively easier, and lid lag disappeared. Aside from these abnormalities of movement, examination of the eyes revealed nothing. This included slit lamp examination.



Fig. 3.—There is marked muscular hypertrophy. The scar is the result of a muscle biopsy.

Myotonia was then found in other muscles, too. After strongly flexing or extending his neck the child had difficulty in straightening it. His gait was abnormally slow and labored. He appeared stiff-jointed. Here the "warming up" phenomenon could be clearly seen; after five or six steps his gait was normal. Myotonia reappeared rapidly if he did not continue to use his muscles.

The myotonia could also be demonstrated after mechanical stimulation of muscle groups. When the thenar eminence of the hand was tapped with a percussion hammer, contraction was rapid and strong, and relaxation delayed. The brachioradial "reflex" was similarly abnormal.

Routine laboratory results were as follows: The routine urinalysis was negative. Blood count showed hemoglobin 14.5 Gm., red blood count 4.27 million, white blood count 5,800, polymorphonuclear leucocytes 28 per cent, lymphocytes 68 per cent. This lymphocytosis persisted on all the examinations. Mazzini test was negative. X-rays of the skull, long bones, neck, lungs, and heart were negative. Carpal and tarsal ossifications were within normal limits. Serum calcium was 10.4 mg. per cent and serum phosphorus 4.5 mg. per cent. Mantoux tests were negative up to 1.0 mg.

Several observations were made on the behavior of the myotonia under a variety of conditions. These experiments were repetitions of experiments previously reported by others in the literature. No attempt was made to record results mechanically or electrically; the evaluation was entirely clinical. Changes that were observed were unequivocal.

1. Electrical reactions: Increased muscle excitability in myotonia had been found previously by Poncher and Woodward.¹ It usually required a galvanic current of 1.8 Ma. to produce a muscular contraction in a normal 6-year-old child. In this patient currents of less than 1.0 Ma. were sufficient.

2. Effects of chilling: It is generally reported that myotonia is worse in cold weather, although Ravin^{2,3} found that myotonia in his patients decreased when the temperature of the environment was reduced from 40° C. to 20° C. Our patient was placed in a cold bath for about ten minutes. He was then moved out into the open air. At this time the myotonia was unchanged, despite the fact that he was shivering with cold.

3. Epinephrine: In the literature there are conflicting reports as to the effect of epinephrine on myotonia. Some investigators report accentuation of symptoms,^{1,4} and others a decrease.^{2,3} In our patient repeated injections of 0.3 c.c. of 1:1000 epinephrine hydrochloride intramuscularly had no effect on the myotonia.

4. Prostigmine: There is a uniformity of opinion that prostigmine accentuates myotonia.⁴⁻⁷ The injection of 1.0 c.c. of 1:2000 prostigmine hydrochloride intramuscularly exaggerated the myotonia in our patient.

5. Quinine: Since 1936,^{4,6,8} quinine has been used as a specific medication in this disease. Small doses often cause a complete disappearance of the myotonia. Our patient was completely relieved of his symptoms by 0.6 Gm. quinine sulfate orally, or 0.5 Gm. quinine dihydrochloride intravenously. The myotonia returned slowly in six hours.

6. Dual nature of the myotonia contraction: This feature of myotonia was commented on by Dana⁹ and Griffith,¹⁰ and has more recently been investigated by Ravin.² The myotonia contraction appears to be initiated by the first strong voluntary contractions, but from then on is independent of them, lasting a definite period regardless of whether relaxation is attempted following these first contractions, or whether a voluntary tetanus is kept up.

The boy was asked to close his eyes tightly for varying lengths of time, after which he was to open his eyes as quickly and as widely as possible. The length of time it took him to open his eyes was recorded. It was found that a minimum period of voluntary contraction was necessary (two seconds) before myotonia appeared. Beyond that minimal period, however, the duration of myotonia was not increased by having the boy squeeze his eyes shut for longer periods. On the contrary it took him less time to open his eyes the longer he kept them closed. When he kept them closed for ten seconds no myotonia was noted on relaxing. This can be interpreted as meaning that the myotonia ran its course under cover of the prolonged voluntary effect.

In summary, a 6-year-old Negro boy presented the classical picture of myotonia congenita. He had pronounced hypertrophy of many of his skeletal muscles, and an inability to relax antagonistic muscles rapidly. Rapid movements thus could not be accomplished. The myotonic delay in relaxation disappeared after several "warming up" contractions. The family history suggested that both the patient's mother and the maternal grandmother suffered from the disease. Observations of the myotonic reaction in this boy, under varying conditions, were consistent with similar observations on cases previously reported in the literature.

SPECIAL STUDIES

A. Search for a Humoral Factor.—The drug veratrine can produce myotonia in normal muscle. An isolated strip of muscles, poisoned with veratrine, behaves remarkably like the muscle of myotonia congenita.¹¹ There is a myotonic pattern of response following stimulation of the nerve. If electromyograms are made from the muscle during the myotonic contraction, it is found that a single shock stimulus in the nerve produces a volley of electrical impulses in the muscle. The veratrine reaction disappears following repeated contraction, or "warming up." Quinine also abolishes the reaction. In all these cardinal points the myotonia of veratrine poisoning resembles that of myotonia congenita. Even in response to curare poisoning the two types of myotonia behave similarly. Curare affects neither (see section B).

In view of this, it seemed reasonable to search for a veratrine-like substance in the blood of patients with myotonia. In 1936 Loewi¹² reported success in finding such a substance in the plasma dialysate of a patient with myotonia congenita. His experiment needed to be repeated. Using essentially the same technique, we attempted this with our patient. The procedure was as follows:

Blood from the external jugular vein was used, because of the prominence of eye signs in this patient. Specimens were also taken from the antecubital vein, before and after tourniquets had been applied. The blood was drawn, heparinized, separated, and frozen until ready for testing. Control specimens were obtained under identical conditions from a normal child. The sartorius muscle of a frog was exposed to (1) the dialysate, and (2) the residue, and was stimulated each time with a galvanic current. The sartorius muscle is usually used for such testing. Characteristic patterns are produced by veratrine in dilutions as high as 1:5,000,000.

No veratrine-like substance could be detected in any of these specimens. A normal twitch resulted in each case.*

An *in vivo* experiment was also tried with this patient, in the hope of demonstrating a myotonia-inducing substance in the blood. The idea for this experiment was taken from the classical one on myasthenia gravis described by Mary B. Walker before the Royal Society of Medicine in 1938.¹³

Tourniquets were placed on the child's arms to obstruct venous return. This was to increase the concentration of such a substance locally. The patient was instructed to open and close his eyes repeatedly until his eye muscles had "warmed up," and all signs of myotonia disappeared. At this point he was asked to open and close his hands several times. Myotonia of the hands was quite evident. The tourniquets were then abruptly removed. It was thought that with the release of this venous blood into the general circulation a myotonia-inducing substance might cause the myotonia of the eye muscles to reappear. No such effect resulted.

We were not able to demonstrate a humoral factor by this *in vivo* experiment.

B. Curarization Experiment.†—In recent years investigators have come to

*We are indebted to Dr. Giulio Cantoni for performing these experiments.

†Dr. Emmanuel Papper supervised the curarization in these experiments.

the conclusion that the site of the abnormality in myotonia is peripheral. However, the exact locus is not known. Kennedy and Wolff⁴ demonstrated that spinal anesthesia does not affect myotonia. Schaffer¹³ showed that myotonia persisted when the nerve endings in the muscles were paralyzed by regional anesthesia. Brown and Harvey⁷ showed that section of the motor nerves and degeneration of the motor end plate did not alter the abnormality. This last work was done with myotonic goats—goats with a congenital disease resembling human myotonia congenita.

Curare is a logical drug to use in carrying this localization further. Curare is said to paralyze muscle through action on the myoneural junction. In an excellent review of the literature, McIntyre¹⁴ pointed out that the chief effect of curarization was a diminution in the end plate potential. Apparently there was also some effect upon the muscle fibers themselves, diminishing their sensitivity to acetyl choline, but this need not concern us. All effects of curare are either upon the myoneural junction or on points distal to it.

In 1939 Brown and Harvey⁷ curarized myotonic goats and found the myotonia uninfluenced by the curare. They reasoned from this experiment that the site of the abnormality in the goats was peripheral to the myoneural junction. There have been no reports of this experiment carried out with a human case of myotonia. Accordingly, with our patient, the following procedure was undertaken:

The patient received nembutal and scopolamine premedication, and was anesthetized with vinyl ether and ether-oxygen mixture. The response after mechanical stimulation of the extensors of the forearm (the brachioradial "reflex"^{**}) was used as an index of myotonia. Motion pictures were taken of all reflexes elicited. After pictures were taken of the "reflex" before curare, curare was given until diaphragmatic contractions stopped.[†] A total of 30 units was used. Respirations were maintained by the anesthetist. Pictures were then taken of the "reflex" under the influence of curare.

We were fortunate to be able to make control observations on a normal child of the same age and weight under identical conditions of anesthesia. Here, too, motion pictures were taken of the brachioradial "reflex" before and after full curarization.

Mechanical stimulation of the extensor muscles of this boy's forearm produced (under anesthesia) a strong contraction with a myotonic delay in relaxation; the hand remained up for several seconds, and only fell slowly to its original position. After complete curarization this response was unchanged. In the normal control the normal brachioradial "reflex" was also uninfluenced by curare.

*The brachioradial "reflex" is not a true reflex in the strict sense of the word. It does not depend upon a reflex arc, and is independent of the central nervous system. It is apparently a direct response to stimulation of the muscle fibers themselves. The persistence of the reflex after curarization is apparent. We have been unable to find any comment on the myotonic reflex in the literature, although it appears to be generally accepted by neurologists.

[†]This degree of curarization is commonly accepted as complete since the diaphragm is the last muscle to be paralyzed.

In human beings with myotonia congenita, therefore, as well as in myotonic goats, curare does not eliminate the myotonic reaction. The abnormality in myotonia must then be peripheral to the site of action of curare. Since, according to our present knowledge, all effects of curare are at the myoneural junction or distal to it, this would put the abnormality in human myotonia somewhere in the muscle fiber itself.

SUMMARY

1. The clinical findings in a case of myotonia congenita (Thomsen's disease) are presented.
2. Attempts at demonstrating a myotonia-inducing substance in the blood of the patient are described. These attempts were unsuccessful.
3. The myotonic pattern of response was uninfluenced by complete curarization of the patient. The significance of this in the localization of the muscular abnormality is discussed.

REFERENCES

1. Poncher, H. G., and Woodward, H.: Pathogenesis and Treatment of Myotonia Congenita, *Am. J. Dis. Child.* 52: 1065, 1936.
2. Ravin, A.: Studies in Dystrophia Myotonica. III. Experimental Studies in Myotonia, *Arch. Neurol. & Psych.* 43: 649, 1940.
3. Ravin, A.: Myotonia, *Medicine* 18: 443, 1939.
4. Kennedy, F., and Wolff, A.: Experiments With Quinine and Prostigmine in the Treatment of Myotonia and Myasthenia, *Arch. Neurol. & Psych.* 37: 68, 1937.
5. Russell, W. R., and Stedman, E.: Observations on Myotonia, *Lancet* 2: 742, 1936.
6. Kolb, L. C., Harvey, A. M., and Whitehill, M. R.: A Clinical Study of Myotonic Dystrophy and Myotonia Congenita, With Special Reference to the Therapeutic Effect of Quinine, *Bull. Johns Hopkins Hosp.* 62: 188, 1938.
7. Brown, G. L., and Harvey, A. M.: Congenital Myotonia in the Goat, *Brain* 62: 341, 1939.
8. Kolb, L. C.: Congenital Myotonia in Goats, *Bull. Johns Hopkins Hosp.* 63: 221, 1938.
9. Dann, C. L.: An Atypical Case of Thomsen's Disease, *M. Rec.* 33: 433, 1888.
10. Griffith, T. W.: On Myotonia Congenita, *Quart. J. Med.* 5: 229, 1911.
11. Krayer, O., and Acheson, G. H.: The Pharmacology of the Veratrum Alkaloids, *Physiol. Rev.* 26: 383, 1946.
12. Loewi, Otto: Personal communication.
13. Schaffer, H.: Zur Analyse der myotonischen Bewegungsstörung, nebst Bemerkungen über die Tonusfunktion des Skelettmuskels, *Deutsche Ztschr. f. Nervenh.* 67: 225, 1920; quoted from Adie, W. J., and Greenfield, J. G.: *Dystrophia Myotonica*, *Brain* 46: 73, 1923.
14. McIntyre, A. R.: Some Physiological Effects of Curare and Their Application to Clinical Medicine, *Physiol. Rev.* 27: 464, 1947.
15. Quoted in Goni, Adalberto R.: *Myasthenia Gravis*, Baltimore, 1946, Williams and Wilkins.

Case Reports

POLYOSTOTIC FIBROUS DYSPLASIA

LOUIS J. HACKETT, JR., M.D., ALBANY, N. Y., AND
WILLIAM M. CHRISTOPHERSON, M.D., NEW YORK, N. Y.

IN 1937 Albright, Butler, Hampton, and Smith¹ described a syndrome characterized by the presence of multiple bone lesions, areas of skin pigmentation, and, in the female, precocious puberty. The term osteitis fibrosa disseminata was suggested to differentiate this entity from osteitis fibrosa generalisata of hyperparathyroidism. Lichtenstein,² in 1938, suggested the entity be designated polyostotic fibrous dysplasia. Since that time, authors³⁻¹⁰ have used various names to designate the condition; of these, Albright's syndrome seems to be the most popular. This would seem fitting because Albright has contributed most to the correlation of the triad, even though isolated cases were reported as early as 1922 by Weil.¹¹ However, Albright¹² suggests that Lichtenstein's term polyostotic fibrous dysplasia be accepted as preferable.

The case reported is a classical example of the complete syndrome of polyostotic fibrous dysplasia, interesting for the unusually early manifestations of precocity.

CASE REPORT

A 5-year-old white female was seen in the pediatric clinic of the Louisville General Hospital on Oct. 28, 1948, with a mild upper respiratory infection. It was evident that her physical development was considerably advanced for her chronological age. Her breasts were prominent and there was a moderate growth of pubic hair. The mother stated that the precocious development had not been a cause of alarm since the child had menstruated on the second day of life and a three-day menstrual period had recurred at regular twenty-eight day intervals since the onset. The breasts were prominent at birth and had steadily enlarged. Four siblings were in good health. The patient was four inches taller than a brother one year older. The child had never been severely ill, was always quiet, bashful and "very nervous," and rarely played with other children.

She walked with a marked limp. There was a swollen ecchymotic area over the anterior aspect of the middle third of the left tibia which had been present for two weeks; it was tender and slightly warm.

There were several areas of dark brown pigmentation over the right half of the trunk. The largest area was on the back; it was not elevated, had an irregular sharply demarcated border, and measured 11 cm. in greatest diameter. Similar, but smaller, areas of pigmentation were noted on the buttock, side, abdomen, and chest. There were no cutaneous or subcutaneous tumors. No areas of pigmentation were found in the mouth. The breasts were adolescent with prominent areolae.

Laboratory Data.—Red blood count was 4.85 million, hemoglobin 80 per cent, white blood count 10,200, polymorphonuclear leucocytes 31 per cent, lymphocytes 64 per cent, monocytes 5 per cent. Urinalysis was normal. Nonprotein nitrogen was 27 mg. per 100 c.c., calcium 11.2 mg. per 100 c.c., phosphorus 4.8 mg. per 100 c.c., alkaline phosphatase 8.4 Bodansky units, serum albumin 5 Gm. per 100 c.c., serum globulin, 2.4 Gm. per 100 c.c.

From the Departments of Pediatrics and Pathology, University of Louisville School of Medicine, Louisville, Ky.

X-ray examination of the skeleton showed multiple areas of "cystlike" lesions involving the humerus, ulna, metacarpals, phalanges, ilium, femur, tibia, and fibula on the left and the femur and fibula on the right (Figs. 1 and 2). The lesions were chiefly hypo-ostotic with only a few hyperostotic areas. There was

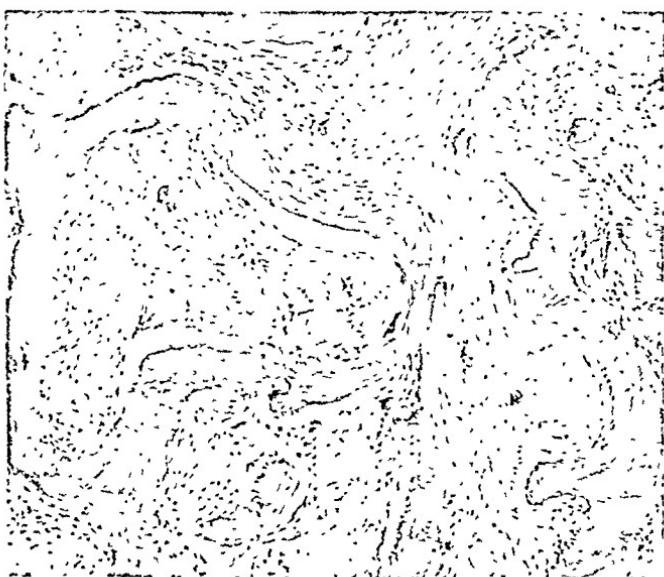


Fig. 1.—Section through medullary canal of left fibula. ($\times 120$.)



Fig. 2.—Irregular area of pigmentation resembling the coast of Maine.

considerable thinning of the cortex in the left tibia, femur, and fibula, with expansion of the fibula. There was a pathologic fracture of the middle third of the left tibia. The epiphyses were not involved and there was no osteoporosis.

A segment of the left fibula was obtained for pathologic examination. The cortex was thinned and the medullary canal was replaced by gritty gray fibrous tissue. Microscopically, the thinned cortex had rather wide Haversian canals which contained fibrous tissue rich in thin-walled vessels. The normal architecture of the medullary canal was completely distorted. Numerous thin poorly-organized septa of new bone with a peripheral zone of osteoid were surrounded by rather cellular mature fibrous connective tissue containing very few thin-walled vascular channels. There were a few collections of osteoclasts at the periphery, and some osteoclastic resorption of the new bone and osteoid tissue. The sections were typical of fibrous dysplasia.



Fig. 3.

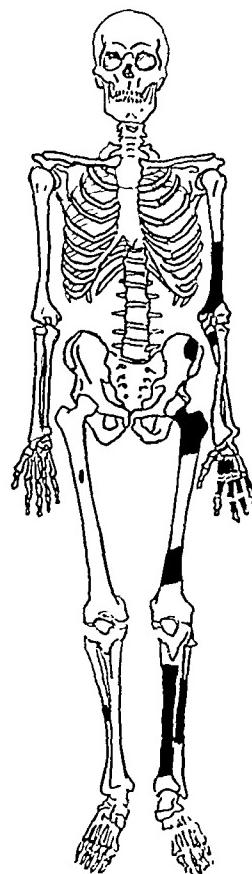


Fig. 4.

Fig. 3.—Lateral view of left tibia and fibula. Pathologic fracture can be seen.
Fig. 4.—Schematic distribution of bone lesions, predominantly on the left.

COMMENT

Such a triad of seemingly dissociated manifestations as are presented in the above case makes the diagnosis of polyostotic fibrous dysplasia one of the more easily recognized syndromes. The differential diagnosis involves consideration of neurofibromatosis, hyperparathyroidism, Ollier's dyschondroplasia,

and xanthomatosis. Since in none of the above conditions do we have similar clinical, radiographic, or pathologic findings, it would seem unlikely that there would be much confusion. However, from the number of patients with indisputable polyostotic fibrous dysplasia who have been subjected to parathyroidectomy,⁴ it appears that the distinction, however easy, is not always made.

Perhaps the most easily confused disease is neurofibromatosis with bone involvement and cutaneous pigmentation. In neurofibromatosis Albright¹² points out that the pigmented areas are shaped like the coast of California rather than the coast of Maine (Fig. 2). In addition, there are usually multiple cutaneous neurofibromata. The bone lesions are relatively few, commonly involving the lower end of the femur and upper end of the tibia, and there are sharply circumscribed areas of destruction with very little, if any, evidence of new bone formation. In polyostotic fibrous dysplasia, on the other hand, there are extensive bone lesions in which overgrowth of bone, as well as bone destruction, is a prominent feature.

Hyperparathyroidism is rare in children, seldom runs such a slow course, and is accompanied by alterations of the serum calcium and phosphorus. Pigmentation and precocious puberty are, of course, lacking; and, finally, the bone lesions are quite different. The bone lesions in fibrous dysplasia have a tendency to be unilateral; the epiphyses are rarely, if ever, involved. Parts of the skeleton appear normal. There are both hyperostotic and hypo-ostotic lesions and there is no osteomalacia. Precocious bone age may be present. Finally, a well-chosen biopsy of the bone will confirm the diagnosis.

Radiographic examination, plus the history and physical examination, with biopsy, if necessary, should clearly differentiate polyostotic fibrous dysplasia from Ollier's dyschondroplasia, and xanthomatosis of bone.

Skin pigmentation is often proportional to the bone involvement and is said to occur on the same side;⁵ however, this is not constant, as indicated in the case reported.

The pathogenesis of the precocity remains unexplained, although the theory that it may be due to lesions in the walls of the third ventricle and the hypothalamus⁵ remains attractive. The autopsy in Albright's Case 3 revealed no evidence that ovulation had ever occurred. Sternberg and Joseph⁹ reported similar findings.

SUMMARY

A case of polyostotic fibrous dysplasia in a 5-year-old girl is reported.

The diagnosis was made by the characteristic triad of predominantly unilateral bone lesions, precocious "puberty," and unilateral skin pigmentation, and was substantiated by radiographic and pathologic examination of the bone lesions.

The early onset of menses (second day of life) is somewhat unusual as is the contralateral distribution of skin pigmentation.

The differential diagnosis is discussed briefly.

REFERENCES

1. Albright, F., Butler, A. M., Hampton, A. O., and Smith, P.: Syndrome Characterized by Osteitis Fibrosa Disseminata, Areas of Pigmentation and Endocrine Dysfunction, With Precocious Puberty in Females. *New England J. Med.* 216: 727, 1937.
2. Lichtenstein, L.: Polyostotic Fibrous Dysplasia, *Arch. Surg.* 36: 874, 1938.
3. Lichtenstein, L., and Jaffe, H. L.: Fibrous Dysplasia of Bone, *Arch. Path.* 33: 777, 1942.
4. Gorham, L. W., Campbell, E. H., Howard, W. P., Donhauser, J. L., and Rust, N. H.: Albright's Syndrome, *Clinics* 1: 358, 1942.

5. Albright, F., Scoville, W. B., and Sulkowitch, H. W.: Syndrome Characterized by Osteitis Fibrosa Disseminata, Areas of Pigmentation and Gonadal Dysfunction, *Endocrinology* 22: 411, 1938.
6. Neller, J. L.: Osteitis Fibrosa Cystica (Albright), *Am. J. Dis. Child.* 61: 590, 1941.
7. Falconer, M. A., Cope, C. L., and Robb-Smith, A. H. T.: Fibrous Dysplasia of Bone With Endocrine Disorders and Cutaneous Pigmentation (Albright's Disease), *Quart. J. Med.* 11: 121, 1942.
8. Dockerty, M. B., Meyerding, H. W., and Wallace, G. T.: Albright's Syndrome, *Proc. Staff Meet., Mayo Clin.* 19: 81, 1944.
9. Sternberg, W. H., and Joseph, V.: Osteodystrophia Fibrosa Combined With Precocious Puberty and Exophthalmic Goiter, *Am. J. Dis. Child.* 63: 748, 1942.
10. Sante, L. R., Bauer, Wm., and O'Brien, R. M.: Polyostotic Fibrous Dysplasia and Its Comparison With Dyschondroplasia, *Radiology* 51: 676, 1948.
11. Weil: Pubertos precox und Kochenbrüchigkeit, *Klin. Wehnschr.* 1: 2114, 1922.
12. Albright, F.: Polyostotic Fibrous Dysplasia: a Defense of the Entity, *J. Clin. Endocrinol.* 7: 307, 1947.

CONGENITAL ATRESIA OF THE INTESTINE IN A PREMATURE INFANT

BEULAH M. KITTRILL, M.D., LEA CALLAWAY, M.D., AND LYNN F. CURTIS, M.D.
MARYVILLE, TENN.

CONGENITAL atresia of the gastrointestinal tract is an extremely rare anomaly occurring, according to most estimates, about once in twenty thousand births. Arnhem¹ tabulated the results of infants treated surgically and reported in the literature from 1911 to 1943. These cases were in infants ranging in age from one hour to 8 days. All were treated by primary anastomosis. Miller² stated that primary anastomosis is the surgical procedure of choice and that primary ileostomy offered absolutely no chance for recovery. That this attitude is well established as authoritative is borne out by a cursory review of the literature.

Erb and Smith³ reported two cases, one with multiple atresias treated by primary anastomosis. Miller, Greengard, Raycroft, and McFadden also reported successful treatment of two cases in this manner. Duncan, Wearn, Jackson, and Waldron⁴ successfully treated multiple atresias in a premature infant by short-circuiting anastomosis. Ficcaro and Degen⁵ reported a patient who died of meconium peritonitis after operation.

James R. Judd⁶ reported the first successful case cured by ileostomy alone. A full-term Chinese female infant showed signs of intestinal obstruction following the first feeding. Surgery was done in four stages. Supportive measures in the form of blood, vitamins, antibiotics, and parenteral fluids were vigorously employed. This case finds a close parallel in the following report in a premature infant treated successfully by primary ileostomy.

CASE REPORT

The child, a female, born at seven and one-half months' gestation, weighed 4 pounds at birth. She was apparently normal except for prematurity and bilateral coloboma.

Immediately after delivery she was placed in an incubator and given continuous oxygen. There was considerable mucus from the posterior pharynx and fluids were withheld until the fourteenth hour, at which time weak tea was given by dropper and continued thereafter every two hours. Some of the feedings were regurgitated but there was no note of actual vomiting. Early on the second morning while the cord dressing was being changed it was noted for the first time that the child's abdomen was greatly distended. She quickly became cyanotic and the pulse was rapid and feeble. X-ray films (Figs. 1 and 2) showed a marked pneumoperitoneum with no air in the large bowel. A diagnosis of perforated viscus was made and immediate exploration was advised. During the subsequent two and one-half hours while awaiting the sacrament of baptism, lactate Ringer's solution was administered subcutaneously and a gastric lavage was performed. Preoperative medication consisted of phenobarbital $\frac{1}{4}$ gr. and atropine $\frac{1}{2500}$ gr. given subcutaneously.

Before taking the patient to surgery a No. 20 needle was inserted into the peritoneal cavity to evacuate the gas which was under such pressure as to severely restrict the motion of the diaphragm. This procedure afforded considerable relief of the respiratory distress, although the child remained cyanotic. Because of the poor condition of the patient the only anesthetic used was novocain $\frac{1}{2}$ per cent supplemented by a sugar teat dipped in bourbon. In view of the fact that it had been impossible to insert a thermometer into the rectum it

From the Departments of Pediatrics, Surgery, and Obstetrics of the Blount Memorial Hospital.

seemed obvious that we were dealing with a congenital anomaly of the rectum. For this reason it was decided to explore the abdomen through a left rectus incision.

A moderate amount of gas escaped when the peritoneal cavity was opened. A fibrous band was found compressing the terminal ileum approximately two inches from the ileocecal valve. Proximal to this point at which the intestine

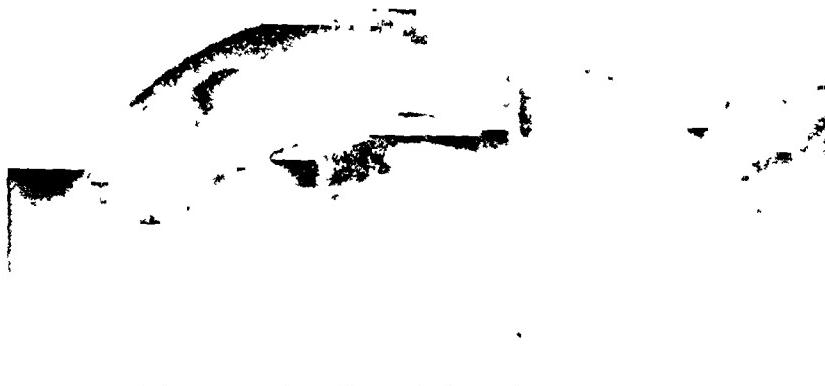


Fig. 1.—Left lateral decubitus.

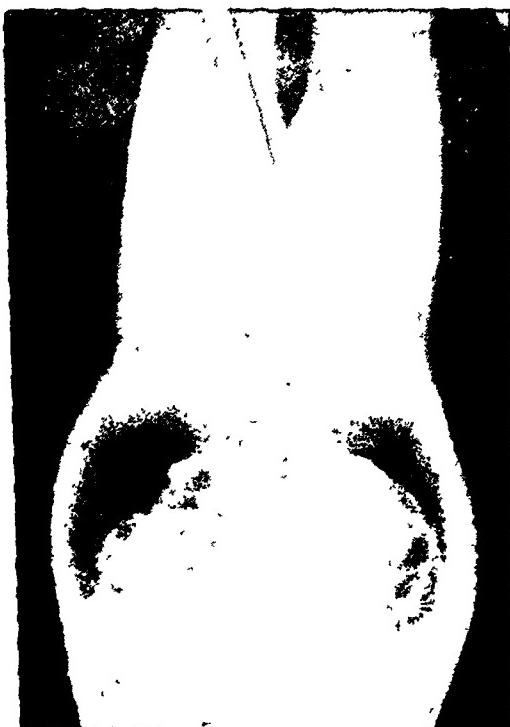


Fig. 2.—Patient Inverted. Inability to insert a thermometer for any distance brought up the question of an imperforate anus. In retrospect it would seem that the cause was due to the tremendous intra-abdominal pressure.

was completely severed, the wall of the bowel was very thin and dilated to a diameter of 3 to 3.5 cm. Distal to the constriction band, the ileum was but a fibrous strand of tissue joining a completely empty cecum, which, like the descending colon, resembled a twisted cord approximately 0.5 cm. in diameter. The gravity of the patient's condition and the very atretic appearance of the colon discouraged further surgery at this time. The dilated end of the ileum was brought out through the lower end of the incision, the peritoneum being closed with continuous catgut and the fascia with interrupted cotton sutures.

The infant was returned to the incubator and continuous oxygen was resumed. Amigen solution with dextrose 5 per cent was given alternately with lactate Ringer's solution subcutaneously every six hours. Breast milk and skinned lactic acid milk of equal parts were started after three hours by dropper feedings. An occasional feeding was vomited during the first thirty-six hours but there was very little abdominal distention at any time. On the third day the child was able to take breast milk from a Breek feeder. After the first week breast milk was unobtainable and Olac, a dried milk mixture of high protein content, was substituted. Ascorbic acid, hypodermatically, and oleum percomorphum were started on the third day, iron in the form of copperin in the formula on the fourteenth day. Parenteral fluids were continued. The discharge from the ileostomy was at first watery and green; by the fifth day it was yellow and gradually becoming pasty. The weight dropped to 3 pounds, 6 ounces, but by the third week had risen to 3 pounds, 9 ounces. At this time the baby was taking formula well and the stools through the ileostomy were normal.

The situation looked pretty hopeless and at the request of the family the baby was discharged to go home in an incubator and be cared for by an aunt who is a graduate nurse. If and when she attained the weight of 7 or 8 pounds it was planned to do x-ray studies to determine the status of the large bowel. The child began to fail as soon as parenteral fluids were stopped. Her weight again dropped to 3 pounds, 6 ounces and remained stationary. Numerous formulas were tried but Olac seemed the most satisfactory. Dehydration was extreme although the average fluid intake was 5 oz. per pound of body weight. The skin surrounding the ileostomy became red and irritated. After three weeks at home she was readmitted to the hospital, a classic picture of marasmus and dehydration.

With the resumption of parenteral fluids the child's general condition began to improve and soon the weight had increased to 5 pounds at which level it became fixed. During this period it was found that the colon could be filled with barium to beyond the hepatic flexure and that the diameter of the bowel was about the size of a lead pencil. Although still a poor risk it was obvious that there would be no further improvement until she was given the benefit of the absorptive surface of the large bowel. The second operation was done at the age of 3½ months.

Through a right rectus incision the fibrous band which represented the terminal ileum was resected with the appendix and the cecum. The ileostomy was freed from the left rectus wound and together with the ascending colon was fixed in the right rectus incision making a double-barreled ileocolostomy after the manner described by Mikulicz. On the third day a clamp was applied to the spur and the process of diverting the fecal stream into the colon was instituted.

The postoperative course was stormy for the first five days, the temperature ranging between 101° and 106° F. The patient was given penicillin in oil daily and sulfadiazine by mouth. Parenteral fluids were continued. On the fifth day there were yellowish green stools from the rectum, but the spill-over from the ileum into the colon was very disappointing, the major portion being discharged onto the abdominal wall. Two weeks after the second operation

it was necessary to restore about four inches of prolapsed ileum to the abdominal cavity. This was done without opening the abdomen by using interrupted cotton to suture the serosa of the ileum to the skin and fascia.

Continued failure to divert the fecal stream into the colon made the closure of the ileocolostomy quite imperative. The first attempt at closure, using interrupted cotton sutures in the fascia, resulted in the same "ignominious failure" described by Dr. Judd. One redeeming feature in the effort was that although the defect was not closed there was no more protrusion of the ileum.

Three weeks later, after daily rectal dilatations and colonic irrigations, a second and successful closure was made. The child at this time was 4½ months of age and weighed 4 pounds, 8 ounces. The usual technique of inverting the intestinal mucosa of the spur with continuous catgut suture reinforced with interrupted cotton sutures was employed. The fascia was again closed with interrupted cotton sutures. The skin was not closed.

The postoperative course was uncomplicated. Stools became normal, parenteral fluids were no longer required, and the child began to gain weight. She was discharged at the age of 5½ months weighing 6 pounds (a gain of 1½ pounds since final closure of the stoma) and was 20 inches long. At the time she was taking evaporated milk, fruits, vegetables, egg yolk, and strained beef.

In addition to the stormy course described, during her hospital stay she had two upper respiratory infections and one bout of pyelitis. The one blood transfusion was given with the greatest difficulty, the veins being no larger than a small pin. The remarkable fact that the lowest blood value obtained showed a red cell count of 3.5 million and 12 Gm. hemoglobin constitutes a tribute to the possibilities of parenteral feeding.

Her subsequent growth and development since discharge from the hospital have been most gratifying. At 7½ months she weighed 9 pounds 12 ounces and was 22½ inches long (a gain of 3 pounds, 9 ounces in two months). At one year of age she weighed 15 pounds and was 25½ inches long. Her tissue turgor was good, she turned from side to side and supported the weight of her body on her palms. Mentally she seemed alert and responsive.

SUMMARY AND CONCLUSIONS

We have presented a case report of atresia of the ileum with rupture and pneumoperitoneum in a premature infant treated successfully by primary ileostomy.

In retrospect it is felt that more careful attention to the colon and its patency contributed largely to the success of the second closure and might have rendered the first successful. While resection and primary anastomosis is the method of choice, this case proves that failure to carry out such a procedure does not preclude the possibility of a successful outcome.

REFERENCES

1. Arnheim, Ernest E.: Congenital Ileal Atresia With Gangrene, Perforation and Peritonitis in Newborn Infant, *Am. J. Dis. Child.* 69: 108-116, 1945.
2. Miller, Edwin M.: Bowel Obstruction in the Newborn, *S. Clin. North America*, p. 73, Feb., 1947.
3. Erb, William H., and Smith, Debert C.: Atresia of the Small Intestine, Two Case Reports, One Multiple Atresia With Survival, *Ann. Surg.* 120: 66, 1944.
4. Miller, Edwin M., Greenguard, Joseph, Raycroft, William B., and McFadden, Irma: Congenital Atresia of the Duodenum and Ileum, *Am. J. Dis. Child.* 66: 272-297, 1943.
5. Duncan, Peter A., Wearn, F., Stafford, Jackson, Herbert F., and Waldron, William S.: Successful Surgical Treatment of Multiple Atresias (Aplasias) of the Small Intestine in a Premature Infant, *J. A. M. A.* 123: 746, 1943.
6. Ficarra, B. J., and Degen, William B.: Congenital Atresia of the Ileum, Spontaneous Perforation and Multiple Intussusception, *Am. J. Surg.* 66: 123-126, 1944.
7. Judd, James R.: Atresia of the Ileum, First Successful Case Cured by Ileostomy Alone, *J. PEDIAT.* 30: 679-685, 1947.

Medical Progress

MALIGNANT NEOPLASMS IN EARLY LIFE

JAMES B. AREY, M.D.
PHILADELPHIA, PA.

THE decline in death rates from infectious diseases, coupled with more accurate diagnoses, has resulted in cancer assuming a progressively more important place as a cause of death in infancy and childhood. In the age group one to 14, cancer, including leucemia and Hodgkin's disease, is now the second-ranking cause of death from disease, and in the age group of 5 to 9 years it accounts for more deaths than any other disease.¹ In Massachusetts in 1939, deaths from cancer in children under 15 years of age exceeded those from pertussis, pulmonary tuberculosis, measles, meningitis, scarlet fever, or diabetes, and almost equaled those from pulmonary tuberculosis, meningitis, and scarlet fever combined.² In New York in the period 1942 to 1944, deaths from neoplastic diseases during childhood exceeded those from all forms of tuberculosis.³ The purpose of the present paper is to point out some of the differences between malignant tumors in early life and those seen in the older age groups, and to review some of the features of the more common malignant neoplasms of infants and children.

The infrequency of carcinomas and the high incidence of sarcomas in early life is striking.^{4, 5, 6} Pack and LeFevre⁵ found sarcoma twenty-two times as frequent as carcinoma in young people less than 25 years of age, whereas if all ages were included, the incidence of carcinoma was almost nine times that of sarcoma.

The malignant neoplasms of early life are frequently radiosensitive, although not, as a rule, radiocurable. In general, they tend to progress rapidly, metastasize widely, promptly recur, and carry a high mortality. Part of the poor prognosis of such tumors, however, is dependent upon ignorance of the physicians and laity as to the occurrence of malignant growths in early life, and is further enhanced by the unfounded assumption that malignant tumors in early life are invariably fatal. Certainly, when compared to the low five-year survival rates of such malignant tumors of adults as carcinoma of the stomach (5 per cent)⁷ and carcinoma of the prostate, the prognosis of many malignant neoplasms of infants and children is actually encouraging. Thus Farber⁸ has reported ten of forty patients with neuroblastoma alive from three to eight years after histologic verification of the tumor, and Ladd and White⁹ report

From St. Christopher's Hospital for Children, and the Departments of Pediatrics and Pathology, Temple University School of Medicine.

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fourteen of sixty patients (23 per cent) with Wilms' tumor alive two to twenty years after treatment. Although such figures are at variance with many of those in the literature, they do indicate that a defeatist attitude when dealing with such neoplasms is not justified.

Certain malignant tumors are found almost entirely in patients in the younger age groups, as medulloblastoma, Wilms' tumor or embryoma of the kidney, retinoblastoma, and neuroblastoma. Others, such as malignant tumors of bone, soft tissues, blood-forming organs, and tumors of the brain, although also occurring in later life, comprise an important part of the malignant tumors of early life. Although tumors have been described in practically all organs of the body at early ages,² the sites most frequently affected by cancer in childhood are the kidneys, the eyes and orbit, the lymphatic and blood-forming organs, the bones, the soft somatic tissues, and the nervous system.³ The tumors occurring in these sites will now be dealt with in more detail.

Wilms' tumor or embryoma of the kidney is one of the commonest abdominal tumors of childhood.¹⁰ It is a tumor peculiar to infancy and childhood, the great majority of these neoplasms appearing in the first three years of life.^{11, 12} The presenting complaint is usually that of an abdominal mass. Fever is present in a significant number of these patients, and a definitely elevated blood pressure may be noted. Hematuria and symptoms referable to the genitourinary tract are far less common than is the case in carcinomas of the renal cortex of adults.

Physical examination reveals a firm, smooth or nodular, nontender mass which may practically fill the entire abdomen. Pyelography reveals distortion of the renal pelvis and calices, displacement of the kidney, and in some instances failure of visualization of the pelvis of the involved kidney. Although pyelograms may be of aid in the differential diagnosis of Wilms' tumor, their greatest importance is in establishing the presence and normality of the opposite kidney, thus preventing the removal of a solitary kidney.

The differential diagnosis includes neuroblastoma of the adrenal, hydronephrosis, mesenteric cyst, and retroperitoneal sarcoma. Although an accurate and correct preoperative diagnosis does much to bolster the ego of the attending physician, attempts to arrive at such a diagnosis should occupy a minimum of time, and repeated, vigorous, and rough palpation of the tumor must be avoided. Final diagnosis must depend upon histologic examination of the tumor, and undue delay in the removal of the tumor in order to arrive at an exact clinical diagnosis should not be condoned.

Grossly, the majority of Wilms' tumors are large, bulky neoplasms which may arise from any portion of the kidney. Nearly all exhibit some degree of encapsulation, the adjoining compressed renal parenchyma often being stretched as a thin layer over the surface of the neoplasm. The cut surfaces are variegated and extensive hemorrhage and necrosis within the tumor may account for the rapid enlargement or sudden appearance of these neoplasms sometimes noted clinically. Involvement of the regional lymph nodes, renal vein, renal pelvis, and ureter should be carefully sought for in order to effect complete removal of the neoplasm.

Histologically, the neoplasm consists of a stroma of loosely or closely packed spindle cells and dark-staining epithelial-like cells having a tubular ar-

rangement; transitions between the epithelial elements and the stromal elements can be demonstrated and strongly suggest a common cell of origin.¹⁰ Glomerularlike structures are sometimes observed. In addition to the above elements, which call to mind the appearance of the embryonic kidney, other "metaplastic" tissues such as smooth and striated muscle, squamous epithelium, and even cartilage may be present.

The treatment of Wilms' tumor consists of nephrectomy plus roentgen therapy. These tumors are radiosensitive, and if the tumor is so large as to make surgical removal unduly hazardous, a preoperative course of irradiation may be used, extending over a period of two to three weeks^{10, 13} followed by nephrectomy and postoperative irradiation.

Although the prognosis of Wilms' tumors is very grave, recent reports have been encouraging. Thus Ladd and White,⁹ in 1941, report that in general these tumors carry a mortality of from 90 to 100 per cent, yet they report a series of 14 of 60 patients (23 per cent) with Wilms' tumors living and well 2 to 20 years after treatment. As recurrences or metastases, if they are to occur, usually do so within two years following nephrectomy, these 14 patients can be considered as probably cured. Nesbit and Adams¹³ report 8 of 16 patients living 3½ to 11½ years after treatment, and Silver¹⁴ reports 10 of 13 patients alive from 2½ to at least 15 years after nephrectomy. One of these patients developed pulmonary metastases 7 months after nephrectomy, for which he received roentgen irradiation to the involved area with rapid disappearance of the lesions; he is alive and well more than 2 years later with no evidence of recurrence. Dickey¹¹ reports 4 of 12 patients alive 4 to 15 years after treatment. Certainly results such as those described above, although still indicative of a very grave prognosis, do not warrant a hopeless outlook with respect to these neoplasms.

The neoplasm probably most frequently confused with Wilms' tumor is the neuroblastoma. These tumors are derived from neuroblasts which have migrated from the neural crest to form the adrenal medulla and the sympathetic ganglia. Thus the neuroblastoma, although commonly arising in the adrenal medulla, may also arise from any of a number of other sites, as the cervical ganglia, the region of the bifurcation of the aorta, and the posterior mediastinum.

These tumors are among the most common malignant neoplasms of infants and children, and may be present at birth.¹⁵ They are usually unilateral, but may involve both adrenal glands. The presenting complain may be that of an abdominal mass or may be referable to the presence of metastases, e.g., in the orbits, bone, or cervical lymph nodes. Skeletal metastases are frequently bilaterally symmetrical and may be found in any part of the skeletal system with the exception of the metacarpal and metatarsal bones and the phalanges.¹⁶

Histologically these neoplasms exhibit varying degrees of differentiation of their neuroblastomatous elements. Thus the more undifferentiated tumors, often referred to as sympathogoniomas, consist of small, round, dark-staining cells with little or no cytoplasm, no fibrillar differentiation, and no pseudo-rosettes. Somewhat more differentiated tumors, sympatheticoblastomas, show the more classical appearance, with many of the cells being arranged in rosettelike

clusters, surrounding a central nonnucleated fibrillar zone made up of fibrils derived from the surrounding cells; no actual lumen is present within these pseudo-rosettes, thus distinguishing them from the true rosettes of the retinoblastoma. Still other more differentiated tumors may show well-differentiated ganglion cells and nerve fibers. Multiple sections may be necessary in order to establish the neurogenic nature of these tumors, and in the past many of them have been referred to as round-cell sarcomas or lymphosarcomas.¹⁷

The treatment of neuroblastoma consists of surgical removal of the primary tumor followed by irradiation. Even in the presence of local metastases, as to the liver, the prognosis is not hopeless and radiation treatment should be tried even when metastases to bone are present.¹⁶ Untreated, the outcome is almost invariably fatal within a few months after the onset of symptoms,¹⁸ although isolated examples of spontaneous maturation of a malignant neuroblastoma into a benign ganglioneuroma have been reported.¹⁹ Farber⁸ has further pointed out that the neuroblastoma may undergo spontaneous hemorrhage and necrosis and disappear without any treatment.

Although an almost hopeless prognosis of neuroblastoma is reported by the majority of authors,^{18, 20} Farber⁸ reports 10 of 40 patients alive from three to eight years after operative discovery and histologic verification of such tumors. Again, as in the case of Wilms' tumor, the prognosis, although very grave, warrants every attempt to effect a cure of these patients.

Retinoblastoma is a rare tumor, occurring only once in about every 34,000 living births.²¹ It is seen almost exclusively in infancy and early childhood, and may be present at birth; from 20 to 30 per cent are bilateral.²² A strong hereditary tendency to the disease has been observed, although the majority of examples observed clinically appear to be sporadic.²¹ However, there is evidence to indicate a probable relationship between the sporadic and the familial types of the disease, so that "sterilization of any child who survives enucleation or irradiation for retinoblastoma and the interdiction of further progeny to the parents of a child with retinoblastoma appear to be justifiable measures."²¹

These tumors are usually first recognized by the presence of a peculiar pupillary reflex, the amaurotic cat's eye reflex, although this may be preceded by dilation of the pupil of the involved eye.²³ Involvement of the opposite eye may be demonstrable at the time of the initial examination or may not become evident for several months, or, rarely, several years. Bilateral involvement is thought to represent multiple primary growths rather than metastatic growth.^{21, 24}

Histologically these tumors consist of small dark-staining cells often collected about blood vessels, with extensive intervening necrosis. Areas of calcification may be present. The most characteristic feature, not present in all tumors nor always present uniformly throughout a given tumor, is the presence of true rosettes. These consist of columnar cells arranged about a central cavity, with their nuclei located at the basilar portion of the rosette. These rosettes are thought to represent developing rods and cones.²⁵

The treatment of retinoblastoma consists of enucleation of the involved eye with removal of as large a portion of the nerve as possible.²² The opposite eye

must be carefully observed for the development of tumor. In the presence of bilateral tumors, when vision remains in one eye treatment may consist of surgical removal of the eye with the more advanced disease and fractionated irradiation of the opposite eye, in an attempt to conserve vision. Using such treatment Martin and Reese²⁴ were able to report two of eight patients living, without recurrence and with vision five years later, and four of the eight patients living without recurrence but blind five years later.

Although intracranial tumors are less frequent in infants and children than in adults,²⁶ they comprise an important group of neoplasms in childhood. Tumors of the central nervous system comprised 44 per cent of 750 cases of malignant disease of children less than 15 years of age observed at the Mayo Clinic between 1921 and 1930.⁴ Tumors of the brain and central nervous system ranked third as a cause of death from malignant disease at ages one to 4 years and second at the age periods 5 to 9 years and 10 to 14 years, according to figures obtained from children insured in the Industrial Department of the Metropolitan Life Insurance Company, from 1943 to 1947.¹

Intracranial neoplasms occurring in infancy and childhood are preponderantly gliomas, and the majority are infratentorial in location. Thus Keith, Craig, and Kernohan²⁷ found that gliomas constituted 84 per cent of the intra-cranial neoplasms in children; 66 per cent of all tumors were infratentorial and 34 per cent were supratentorial.

The most constant and one of the most important symptoms of an intra-cranial neoplasm in children is vomiting. Contrary to common belief, such vomiting is usually not projectile in nature and is often associated with nausea. The initial symptoms, therefore, are often erroneously interpreted as a "gastro-intestinal upset," and their underlying cause may go unrecognized for several months. Delay in diagnosis is further enhanced by the fact that the nausea and vomiting are often intermittent in character, occurring every morning for a period of several days, then disappearing and leaving the child in apparent good health, only to recur at a later date in a more persistent form. Several such episodes may occur before an intracranial neoplasm is suspected. Headache, although less constant in children than in adults, is another important symptom of an intra-cranial neoplasm. Enlargement of the head, strabismus, diplopia, and papilledema are other signs and symptoms common to many intracranial neoplasms, regardless of their location. Localizing symptoms will be mentioned only briefly. In general, posterior midline cerebellar tumors tend to give rise to staggering and uncertainty of gait, the signs of cerebellar dysfunction being most marked in the trunk and lower extremities and being largely the result of a disturbance of equilibrium.²⁶ Tumors of the cerebellar hemispheres tend to give rise to much more marked cerebellar dysfunction, usually more severe on the side of the tumor, and produce disturbances of voluntary muscular activity in the form of asynergy and slowness of movement, readily manifested by the finger-to-nose and heel-to-knee tests and by the presence of adiakokinesis.²⁶ Tumors of the brain stem may not give rise to increased intra-cranial tension and do give rise to palsies of one or more of the cranial nerves. Because of the

absence of increased intracranial pressure such neoplasms are often misdiagnosed as encephalitis.²⁶

The astrocytoma is the most common intracranial neoplasm in children, comprising about 25 per cent of intracranial tumors. In contrast to adults, where such neoplasms occur predominantly in the cerebral hemispheres, in children the vast majority are located in the cerebellar hemispheres or in the vermis of the cerebellum. Grossly they are firm, pale, avascular tumors which may appear to be quite well circumscribed. They may be solid, may contain multiple cystic areas, or may consist of a large fluid-filled cyst with a mural nodule. Histologically they consist of fairly mature astrocytes which may be principally protoplasmic or fibrillary.²⁸ Numerous fibrils are present between the widely separated cell bodies of the fibrillary astrocytoma; these fibrils may be largely absent in the protoplasmic type.

Cerebellar astrocytomas offer the best prognosis of the intracranial gliomas of childhood. They are generally slowly growing tumors, but tumors involving the vermis may give rise to an abrupt onset of symptoms of increased intracranial pressure and may be indistinguishable clinically from the more rapidly growing medulloblastomas. Simple removal of the fluid from the cavity of a cystic astrocytoma may give relief from symptoms for varying periods of time, but removal of the mural nodule or extirpation of the tumor is necessary in order to affect a cure.

The results in the treatment of cerebellar astrocytomas are truly encouraging. Of twenty patients with cerebellar astrocytomas surgically treated by Bailey, Buchanan, and Bucy, 80 per cent living one to eight years later, the majority of these well, the others with varying degrees of disability, including total blindness.²⁸

Medulloblastoma is the next most frequent intracranial tumor of childhood, accounting for 20 per cent of the neoplasms.²⁷ These tumors are almost exclusively midline cerebellar tumors, usually occurring at a somewhat younger age than the cerebellar astrocytomas²⁷ and affecting boys more frequently than girls. They comprised 16.2 per cent of 281 gliomas occurring in the military age group.²⁹ Of all of the tumors of the brain these are the most prone to give rise to multiple implants of tumor tissue in the meninges of the cranial cavity and within the spinal meninges. They cannot always be distinguished clinically from cerebellar astrocytomas involving the vermis, but the rapid progression of symptoms may at times aid in the differential diagnosis.

Histologically these tumors, which arise from the vermis of the cerebellum or the region of the roof of the fourth ventricle, consist of round or oval cells with scanty cytoplasm, usually arranged as a structureless mass but occasionally showing an arrangement of the nuclei in the form of pseudo-rosettes. According to Bailey and Cushing³⁰ these tumors are derived from undifferentiated cells or medulloblasts and contain numerous spongioblasts and a smaller number of neuroblasts. Roussy and Oberling,³¹ however, feel that the predominant element of the tumor is the neuroblast and prefer to classify these tumors as neuro-spongiomas. Regardless of the origin of these cells, sections from the more

undifferentiated areas may, at least with hematoxylin and eosin stains, be indistinguishable from the highly undifferentiated areas of neuroblastomas or retinoblastomas, tumors also derived from immature neural tissue.

Medulloblastomas are radiosensitive but not as a rule radiocurable. Although their growth may be checked for a considerable period of time by radiation therapy, they ultimately result in the death of the patient.²²

Ependymomas comprise about 10 per cent of the intracranial neoplasms in children. These tumors usually arise from the floor of the fourth ventricle and give rise to symptoms often indistinguishable from those of the midline cerebellar medulloblastomas. Histologically they are characterized by the radial arrangement of their cells about vascular spaces; the radially arranged nuclei are located at a considerable distance from the central vessel, the intervening region being filled with the processes of the cells. Although these tumors are histologically relatively benign, their location is such that attempts at operative removal carry a high mortality and their ultimate prognosis is poor.

Gliomas of the brain stem constitute approximately 15 per cent of the intracranial tumors of children.²⁶ Histologically these may show the structure of polar spongioblastoma, astrocytoma, or glioblastoma multiforme. Because of the frequent absence of increased intracranial pressure, these tumors are often erroneously diagnosed as encephalitis. Although many of them are relatively benign histologically, their location makes operative removal impossible.

Malignant tumors of bone feature prominently as a cause of death in later childhood. The majority occur between the ages of 10 and 25 years; males are affected more frequently than females. For practical purposes malignant bone tumors in children may be divided into osteogenic sarcoma and Ewing's tumor of bone. Although these are distinctly different pathologic entities, it must be remembered that clinical and roentgenologic differentiation between these neoplasms is not always possible.

Osteogenic sarcoma usually begins in the metaphyseal region of the long bones, the lower end of the femur and the upper end of the tibia being the sites most frequently involved. The initial symptom is pain, which may be intermittent and nocturnal in character and may precede the clinically palpable tumor by a period of weeks or months. Persistent pain in a long bone should suggest the possibility of a malignant tumor of bone. A history of trauma to the effected part is frequently elicited but it is usually impossible to prove an etiologic relation between trauma and the neoplasm in any given case. Fever may be present, although this is more frequent in Ewing's tumor of bone than in osteogenic sarcoma.

Roentgenologic examination is of inestimable value in the diagnosis of malignant tumors of bone, and frequently a strongly presumptive diagnosis of the type of lesion can be made prior to histologic examination of the neoplasm. However, it is important to remember that the shadows cast by benign lesions of bone may closely simulate those of malignant bone tumors, and a positive diagnosis should not be made and therapy should not be carried out until the true nature of the lesion has been determined by biopsy and histologic examination of the removed tissue. It is as important, moreover, for the pathologist to have the

assistance of a competent radiologist as is the reverse, and erroneous diagnoses may well be made by the pathologist who has not availed himself of the assistance of a competent radiologist or who has not himself examined the roentgen-ray films. Such benign lesions as fibrous dysplasia of bone or even a healing fracture may give a histologic appearance not unlike that of osteogenic sarcoma. The pathologist, then, who takes it upon himself to interpret biopsies from suspected bone tumors, should avail himself of all clinical data pertaining to the case, including the study and interpretation of the roentgen-ray plates.

Much confusion has arisen from the term osteogenic sarcoma, which has been interpreted as referring to a bone-forming tumor. Although some bone production is usually present in such tumors, it is important to remember that osteogenic sarcoma refers to a tumor derived from bone, or, more strictly, a sarcoma derived from ancestors of cells which, when duly differentiated, are known as osteoblasts.³³ These cells may, therefore, cease their differentiation at any point from primitive mesenchyme through the normal sequence of differentiation of bone to fibroblast, cartilage cell, or osteoblast, with resultant variations in the histologic pattern of the tumor. The intercellular matrix may also vary from a myxomatous type of tissue to collagenous, cartilaginous, osteoid, or calcified osseous tissue. Attempts to separate the osteogenic sarcomas into different categories on the basis of their constituent types of cells or matrix, or even on the basis of their gross anatomic location in the bone, are usually of little or no clinical or prognostic value, and the tumors are probably best considered simply as osteogenic sarcomas with a careful gross and microscopic description appended for future reference, study, and conceivably, a more detailed classification.

The treatment of osteogenic sarcoma is amputation, and no more difficult task confronts the pathologist or surgeon than to recommend and carry out amputation in a child often in apparently good health. The task is made even more difficult by realization of the extremely poor prognosis even after amputation. Because of the few recorded five-year survivals in patients under the age of 10 or 12 years who were treated by radical surgery alone or by irradiation alone, Coley³⁴ recommends a thorough course of preoperative irradiation followed promptly by amputation in young patients (but not in adults).

Ewing's tumor of bone may be indistinguishable from osteogenic sarcoma both clinically and roentgenologically. Characteristically it begins in the shaft of a long bone rather than the metaphyseal region, giving rise to a fusiform enlargement of the shaft. The tumor perforates the cortex, where it stimulates the production of new periosteal bone in successive layers, giving rise to the typical "onion skin" appearance seen in the roentgen ray plate. It should be emphasized that this newly formed bone is reactive in nature, not neoplastic, and that a similar roentgenologic picture can be produced by nonneoplastic conditions. Metastases occur in the lungs, regional lymph nodes, and other bones, so that multiple bone lesions are common at the time of autopsy. This is at variance with osteogenic sarcoma where involvement of more than one bone is rare.

The clinical picture of Ewing's tumor of bone may be confused with that of osteomyelitis, a history of trauma, fever, leucocytosis, and pain being common to both. Even at the time of biopsy differentiation may not be easy, as

the small, dark cells of a Ewing's tumor may be confused with the inflammatory cells of osteomyelitis. Ewing's tumor is characterized by sheets of small, dark-staining, round or slightly ovoid cells with little cytoplasm and no evidence of formation of bone by the tumor cells; mitotic figures may be numerous but giant cells and pleomorphism are uncommon. The histologic appearance may resemble that of neuroblastoma, and indeed Willis²⁵ feels that many such tumors are actually metastatic neuroblastomas.

Ewing's tumors are radiosensitive but following radiation recurrences often occur and the tumor becomes radioresistant. Amputation or resection immediately following the period of maximum radiation response is probably the treatment of choice,²³ although immediate amputation is carried out by others. Unfortunately, as with osteogenic sarcoma, few five-year survivals can be expected.

No attempt will be made to deal with Hodgkin's disease, lymphosarcoma, and sarcomas of soft tissues, as these neoplasms have their counterparts in adult life. No attempt will be made to cover the subject of leucemia, the most common fatal type of cancer in children, as this is a subject too broad for the scope of the present paper. Suffice it to say that leucemia in childhood is usually of the acute type. The initial symptoms may be those of an acute infectious process, hemorrhagic phenomena, or bone and joint pain which may simulate rheumatic fever. Changes in the peripheral blood are often inadequate for diagnosis, and bone marrow aspiration is probably always indicated before institution of therapy. Recent studies^{26, 27} have indicated that Aminopterin and related compounds may produce temporary but significant clinical, hematologic, and bone marrow remissions in patients with acute leucemia. However, the severe toxic effects of these drugs and the fact that they merely produce remissions, not cures, must be remembered. Although of value in the treatment of leucemia, their greatest value appears to be toward further research on the fundamental nature of the neoplastic cells.

SUMMARY AND CONCLUSIONS

Malignant disease is one of the most important causes of death in children under 15 years of age. Although in general, malignant tumors in early life carry a very grave prognosis, many cases can be cured by prompt diagnosis and early therapy. Although some forms still have a hopeless prognosis, cure rates in others prove that the defeatist attitude exhibited by so many when dealing with malignant tumors in childhood is not justified.

REFERENCES

1. Cancer Among Children, Statist. Bull. Metrop. Life Insur. Co. 30: 1-4, 1949.
2. Williams, I. G.: Cancer in Childhood, Brit. J. Radiol. 19: 182-197, 1946.
3. Dargeon, H. W.: Cancer in Children from Birth to Fourteen Years of Age, J. A. M. A. 136: 459-468, 1948.
4. Helmholtz, H. F.: Malignant Neoplasms in Childhood, Proc. Int. State Soc. Med. N. America, pp. 209-211, 1931.
5. Pack, G. T., and LeFevre, R. G.: The Age and Sex Distribution and Incidence of Neoplastic Diseases at the Memorial Hospital, New York City, with Comments on "Cancer Ages," J. Cancer Research 14: 167-294, 1930.
6. Schultz, O. T.: Tumors of Infancy and Childhood, in Abt, I. A.: Pediatrics, vol. 8. Philadelphia and London, 1926, W. B. Saunders Company, pp. 641-865.

7. Moore, R. A.: *A Textbook of Pathology*, Philadelphia and London, 1945, W. B. Saunders Company, p. 831.
8. Farber, S.: Neuroblastoma, *Am. J. Dis. Child.* 60: 749-751, 1940.
9. Ladd, W. E., and White, R. R.: Embryoma of the Kidney (Wilms' Tumor), *J. A. M. A.* 117: 1858-1863, 1941.
10. Weisel, W., Dockerty, M. B., and Priestley, J. T.: Wilms' Tumor of the Kidney; A Clinicopathologic Study of Forty-Four Proved Cases, *J. Urol.* 50: 399-413, 1943.
11. Dickey, L. B., and Chandler, L. R.: Embryoma of Kidney (Wilms' Tumor) in Children, *Pediatrics* 4: 197-200, 1949.
12. Ewing, J.: *Neoplastic Diseases. A Treatise on Tumors*, ed. 3, Philadelphia and London, 1928, W. B. Saunders Company, p. 796.
13. Nesbit, R. M., and Adams, F. M.: Wilms' Tumor; A Review of Sixteen Cases, *J. PEDIAT.* 29: 295-303, 1946.
14. Silver, H. K.: Wilms' Tumor (Embryoma of the Kidney), *J. PEDIAT.* 31: 643-650, 1947.
15. Wells, H. G.: Occurrence and Significance of Congenital Malignant Neoplasms, *Arch. Path.* 30: 535-601, 1940.
16. Wyatt, G. M., and Farber, S.: Neuroblastoma Sympatheticum; Roentgenological Appearances and Radiation Treatment, *Am. J. Roentgenol.* 46: 485-495, 1941.
17. Willis, R. A.: *Pathology of Tumors*, London and St. Louis, 1948, Butterworth & Co., Ltd., and C. V. Mosby Company, p. 843.
18. Redman, J. L., Agerty, H. A., Barthmaier, O. F., and Fisher, H. R.: Adrenal Neuroblastoma; Report of a Case and Review of the Literature, *Am. J. Dis. Child.* 56: 1097-1112, 1938.
19. Cushing, H., and Wolbach, S. B.: Transformation of a Malignant Paravertebral Sympathicoblastoma Into a Benign Ganglioneuroma, *Am. J. Path.* 3: 203-216, 1927.
20. Blacklock, J. W. S.: Neurogenic Tumors of Sympathetic System in Children, *J. Path. & Bact.* 39: 27-48, 1934.
21. Weller, C. V.: The Inheritance of Retinoblastoma and Its Relationship to Practical Eugenics, *Cancer Research* 1: 517-535, 1941.
22. Duke-Elder, W. S.: *Textbook of Ophthalmology*, vol. 3, St. Louis, 1941, C. V. Mosby Company, pp. 2812-2843.
23. Dargeon, H. W.: *Cancer in Childhood and a Discussion of Certain Benign Tumors*, St. Louis, 1940, C. V. Mosby Company, p. 69.
24. Martin, H., and Reese, A. B.: Treatment of Bilateral Retinoblastoma (Retinal Glioma) Surgically and by Irradiation; Report on Progress, *Arch. Ophth.* 33: 429-439, 1945.
25. Wolff, E.: A Note on the Rosettes, Nature and Nomenclature of "Glioma Retinae," *Brit. J. Ophth.* 28: 448-450, 1944.
26. Bailey, P., Buchanan, D. N., and Bucy, P. C.: *Intracranial Tumors of Infancy and Childhood*, Chicago, 1939, University of Chicago Press.
27. Keith, H. M., Craig, W. M., and Kernohan, J. W.: Brain Tumors in Children, *Pediatrics* 3: 839-844, 1949.
28. Bailey, P., and Cushing, H.: A Classification of the Tumors of the Glioma Group on a Histogenetic Basis With a Correlated Study of Prognosis, Philadelphia, London, and Montreal, 1926, J. B. Lippincott Company, pp. 84-87.
29. Bennett, W. A.: Primary Intracranial Neoplasms in Military Age Group—World War II, *Mil. Surgeon* 99: 594-652, 1946.
30. Bailey, P., and Cushing, H.: Medulloblastoma Cerebelli; A Common Type of Mid-cerebellar Glioma of Childhood, *Arch. Neurol. & Psychiat.* 14: 192-224, 1925.
31. Roussy, G., and Oberling, C.: Histologic Classification of Tumors of the Central Nervous System, *Arch. Neurol. & Psychiat.* 27: 1281-1289, 1932.
32. Bailey, P.: Further Notes on the Cerebellar Medulloblastomas; The Effect of Roentgen Radiation, *Am. J. Path.* 6: 125-136, 1930.
33. Kolodny, A.: Bone Sarcoma. The Primary Malignant Tumors of Bone and the Giant Cell Tumor, *Surg., Gynec., & Obst.* 44: 1-214, Apr. (Pt. 2), 1927.
34. Coley, B. L.: Neoplasms of Bone and Related Conditions: Their Etiology, Pathogenesis, Diagnosis, and Treatment, New York, 1949, Paul B. Hoeber, Inc., p. 258.
35. Willis, R. A.: Metastatic Neuroblastoma in Bone Presenting the Ewing Syndrome, With a Discussion of "Ewing's Sarcoma," *Am. J. Path.* 16: 317-332, 1940.
36. Farber, S., Diamond, L. K., Mercer, R. D., Sylvester, R. F., and Wolff, J. A.: Temporary Remissions in Acute Leukemia in Children Produced by Folic Acid Antagonist 4-aminopteroyl-glutamic acid (Aminopterin), *New England J. Med.* 238: 787-793, 1948.
37. Farber, S.: Some Observations on the Effect of Folic Acid Antagonists on Acute Leukemia and Other Forms of Incurable Cancer, *Blood* 4: 160-167, 1949.

Psychologic Aspects of Pediatrics

SELF-REGULATION AND THE MOTHER

HARRY BAKWIN, M.D.
NEW YORK, N. Y.

AMERICAN pediatrics has rejected traditional methods of child rearing and has adopted instead an attitude toward child care which is based on developmental principles. The child's maturing needs and capabilities are to be the guides to management. Each child is viewed as an individual whose pattern of development fits, in a general way only, the development of children as a whole. Training procedures for self-feeding, toilet, etc., are introduced when the individual child is ready to be trained and not according to a pre-arranged time schedule.

This point of view seems reasonable and sensible. It should make childhood happier, child rearing easier, and, perhaps, prevent a certain amount of emotional difficulty in later life. It is an approach which places the responsibility for making decisions about the child largely on the mothers. They, not the doctor or the book, are to decide, from the baby's behavior, when he is to eat and how much, how long he is to be allowed to cry, when he is to be toilet trained, and so on.

The success of the modern approach depends, to a large extent, on the personality of the mother (as well as that of the child) and her reaction to self-regulation. Unfortunately, there are many mothers to whom the task of individualizing child rearing is a source of great anxiety. Themselves reared according to rigid regimens, they have, perhaps, taken courses in child psychology and read books on the subject, and they are imbued with the idea that bringing up a child is a highly complicated science. Telling them that child rearing is actually a very simple process, carried out successfully by millions of very simple people, pointing out that the most desirable attitudes toward a baby are the unlearned attitudes that adults intuitively assume, urging them to be natural with their baby; these are of little or no avail. Some of these mothers are too young, others too old. Some are overly anxious because of the loss of a previous child, or because of a serious illness or a defect in a previous child or in the child of a near relative or a friend. In other instances, the mother's emotional difficulties are more deep-seated, and parenthood simply gives direction to her inner tensions. But most of them are quite normal as indicated by their much more relaxed attitude toward subsequent children. Unaided by the sanction of a traditional approach, they are overwhelmed by a task which they are, for the time being, unable to handle.

There are other mothers to whom self-regulation is distasteful. Some have had a certain amount of experience in the business world and derive great satisfaction from receiving precise prescriptions for feeding, sleep, toilet training, etc. (the "orderly type"). Still another group consists of women who are by nature dominating or bossy (the "executive type"). They like to feel themselves in command of every situation. They generally accept the physician's prescriptions calmly and then proceed to disregard them, doing things their own way. They have little difficulty while their children are babies; only later on, when they encounter a child whose emotional make-up is modeled after their own, does the clash of personalities lead to trouble.

In giving advice regarding child rearing, then, the physician must take into consideration the parental personalities, particularly that of the mother. The method of child rearing must suit the maternal temperament and cultural background. Individualization is fully as necessary in dealing with the mother as it is with the child. If the physician is convinced that self-regulation is going to make the mother overly anxious or otherwise unhappy, more or less specific directions should be given. An approach which she finds uncongenial will not only disturb her emotionally, it will make her task more difficult and will probably create unnecessary tensions in the child. It is unwise to try to coerce a mother who, by training, previous experience, or temperament, needs detailed instructions. Insistence that she take on, at once, the full responsibilities implied in motherhood serves only to increase her uncertainty, to undermine her self-confidence, and to lessen her efficiency.

It is well to remember that children reared by methods far different from ours, grow up to be adults who are, according to general observation (the only available standard), fully as happy and stable as we. Every country, every culture, has its own unique way of bringing up children which, in the main, is based on tradition. These different methods are, to a large extent, expressions of national or cultural ideals.

A systematic study of child rearing in certain central and eastern European cultures was recently carried out in New York City by Benedict.¹ In contrast to the current American practice of allowing babies freedom of movement from the time of birth, it is the custom among the peoples of eastern Europe to swaddle babies. Swaddling is tightest and is continued longest in Russia. The bundled baby is kept as rigid as if he were bound to a board. Sometimes the lashing is so tight that respiration is interfered with and strangulation is averted only by loosening the bindings. The swaddling is considered to be necessary for the safety of the infant who is regarded as being in danger of destroying himself. The baby must be confined for his own sake and his mother's. However, he is not isolated. He is kept where adults are congregated and he is talked to and carefully cared for. Swaddling is continued for nine months, sometimes longer.

The restriction does not relate to the emotions, however. Since the baby's principal means of grasping the outside world is through the eyes, it is significant that in Russian speech and literature great emphasis is placed on the eyes, as "mirrors of the soul."

An interesting feature of child rearing in Russia is the diffuseness of relationship between child and adults. The child's contact during the first year of life is not limited to the mother but is spread among many adults such as wet nurses, older women who are engaged to care for the baby, and others. Consequently the theme of mother love is practically nonexistent in Russia. Nursing and toilet training are warm and permissive.

The Polish attitude toward swaddling is quite different from the Russian. The infant is looked upon as fragile, not violent, and the bindings are applied to give the baby support and to keep his legs straight. Swaddling is regarded as the first step in a long process of "hardening"; and since one is hardened by suffering, suffering is also highly prized. Crying is good for a baby because it strengthens the lungs, and beating a child is also good, for it too "hardens" the child.

Another purpose of swaddling in Poland is to keep apart the clean and dirty parts of the body. The binding prevents the baby from putting the toes in the mouth—the feet in Poland are viewed as shame-ridden as the genital organs—and it keeps the baby from touching his face with the fingers which may just before have touched his crotch or his toes.

Whereas weaning is gradual in Russia, the baby receiving chewed bread at an early age and other foods later on while still nursing, the process in Poland is sudden. The Polish baby is not given an opportunity to accustom himself to solid food until he is taken off the breast; the sudden transition is good because it is "hardening."

The Russian custom of having many adults care for the baby is not practiced in Poland. Only the mother can touch the baby without danger of harming him.

Jewish babies in Poland and the Ukraine are also swaddled. The binding includes a soft pillow and the wrappings are rather loosely applied. As she swaddles the baby the mother generally sings to him. The specific stress is on warmth and comfort and the restriction is regarded with pity and commiseration. Swaddling is also viewed as insuring straight legs. It is in no sense considered the beginning of a "hardening" process or as necessary because the baby is inherently violent.

Strange as these customs may seem to us, it is well to keep in mind that, as nearly as one can observe, they have not been psychologically traumatic in the long run. There are many ways of bringing up children. It is becoming increasingly clear that the deviations from the principles of child rearing which we have come to accept are less important, so far as their effects on the child are concerned, than is the state of mind or the general attitude of the parent toward the child. Commenting on Benedict's report, Mead² says that too early toilet training, carried out for some casual reason of household management, may have an almost negligible effect on the child, while the same procedure at the proper developmental stage may, because of the emphasis given to it by the mother, be a much greater trauma.

Advice to parents, then, must be tempered by an appreciation of their personalities, their experiences, and their cultural background. This is not

to say that we are to yield readily to mothers who prefer to shift their maternal responsibilities on to the physician. Most of us find it easier to take orders than to make decisions. Parenthood, after all, necessitates taking responsibility and parents will do well to learn this lesson early. But the physician will need to discriminate between those mothers who are ready for self-regulation and those who need the extra support which they get from more or less precise prescriptions.

REFERENCES

1. Benedict, R.: Child Rearing in Certain European Countries, *Am. J. Orthopsychiat.* 19: 342, 1949.
2. Mead, M.: *Ibid.*, p. 349.

Comments on Current Literature

BACITRACIN IN LOCAL TREATMENT OF PYOGENIC INFECTIONS

BACITRACIN, a chemotherapeutic substance isolated from a sporulating bacillus of the *Bacillus subtilis* group,¹ was identified as a diffusible polypeptide possessing antibiotic activity against a variety of gram-positive bacteria and against spirochetes. Early experimental studies in animals showed that bacitracin is absorbed slowly and that it is excreted by glomerular filtration. Its therapeutic potentialities seemed favorable. Further investigations, however, revealed that renal lesions were produced in animals where large doses were administered. Since these toxic renal manifestations were not correlated with the antibacterial potency of different samples of bacitracin, it seemed likely that the toxicity might be due to impurities, and further efforts were made to refine the substance.

In human subjects cautious clinical trials with bacitracin administered systemically gave reasonably good therapeutic results, but here again transient albuminuria and other signs of nephrotoxicity damped enthusiasm for its general use, particularly in view of the fact that penicillin and bacitracin have an antibacterial spectrum which is almost identical.

However, safe, effective agents for local therapy in pyogenic infections of the skin constitute a real need, and for this purpose bacitracin is proving particularly suitable. Meleney and Johnson² in 1947 reported favorable results with bacitracin in the topical treatment of 100 cases of surgical infection, including a variety of types. Solutions or ointments containing 10 to 100 units of bacitracin per milliliter were used. Eighty-eight per cent of these infections responded to treatment, even when some of the gram-positive organisms isolated from the area were shown by culture studies to be penicillin-resistant streptococci or staphylococci.

More recently Miller, Slatkin, and Johnson³ have reported the results of a careful evaluation of bacitracin in local treatment of pyogenic infections. Various base preparations were used as ointments, containing varying concentrations of bacitracin. In the laboratory and clinical appraisal of these preparations three features were considered: the physical properties of the base preparation, the stability of the antibiotic when incorporated in the ointment, and the release of the bacitracin content. Of fourteen ointment bases tried, three were definitely superior:

Base No. 2	Carbowax 1540	50 Gm.
	Carbowax 200	50 Gm.
	Carbowax 4000	25 Gm.
Base No. 8	Cetyl alcohol	10 Gm.
	Glycerin	10 Gm.
	Sodium lauryl sulfate	1 Gm.
	Distilled water	74 c.c.
Base No. 10	Lanette wax	20 Gm.
	White petrolatum U.S.P.	20 Gm.
	Liquid petrolatum U.S.P.	20 c.c.
	Distilled water	30 c.c.

Bacitracin was added to each ointment base, 500 units per gram being incorporated in some samples and 1,000 units in others. The ointments remained stable and therapeutically effective for at least two weeks without refrigeration. By laboratory tests oil-in-water and greaseless carbowax bases were found best for stability and for release of bacitracin.

The majority of the patients studied were seen in the Outpatient Clinic. In all cases bacterial cultures of the lesions were taken before treatment in order to identify the causative organism and test its sensitivity to bacitracin. Of sixty-eight patients treated for primary superficial skin infections, fifty responded favorably. In eighteen patients, eleven of whom had folliculitis of the beard, the therapeutic response was unsatisfactory. However, in six of these so-called failures, all of whom had folliculitis of the beard, the infection was kept under control and the area free of lesions so long as the ointment was used daily. The remaining seven instances of failure included one case of infectious eczematoid dermatitis, three cases of vesiculopustular eruption of the hands, one folliculitis elsewhere than of the beard, and two cases of perifolliculitis capitis.

Another group included in this outpatient study comprised patients with dermatoses complicated by secondary bacterial infection. While the secondary bacterial infection was cured in this group, bacitracin ointments were of no value against the primary dermatoses.

No better clinical results were obtained in any of the cases with ointments containing 1,000 units of antibiotic per gram than with those containing 500 units per gram.

On the basis of their experience the authors conclude that bacitracin is an effective agent for local therapy in pyogenic infections of the skin. Its effectiveness approximates that of penicillin, the sulfonamide drugs, and nitrofurazone, and its real superiority consists in the low rate of sensitization of the patient, one-half of one per cent sensitization being recorded thus far. This situation is in contrast to the findings with penicillin where 6 per cent of patients were sensitized, and with sulfonamides and nitrofurazone, where 5 per cent were sensitized to the drugs. No cutaneous reactions to bacitracin have been reported. In one patient this antibiotic in ointment form was applied daily for 300 days with no evidence of cutaneous sensitization.

While bacitracin is toxic when administered parenterally, this is not the case apparently when it is used as a local therapeutic agent, even where the ointment is applied over widespread areas of the body surface. If more evidence is added that such is the case and that sensitization on prolonged use is minimal, the advantages of local bacitracin are obvious. Where patients develop sensitization to other agents such as penicillin and sulfa drugs, and particularly where the causative organisms become resistant to these medications, bacitracin may be of considerable importance in the local therapy of skin infections.

RUSSELL J. BLATTNER.

REFERENCES

1. Johnson, B. A., Anker, H., and Meleney, F. L.: A New Antibiotic Produced by a Member of the *B. subtilis* Group, *Science* 102: 376, 1945.
2. Meleney, F. L., and Johnson, B. A.: Bacitracin Therapy: The First Hundred Cases of Surgical Infections Treated Locally With the Antibiotic, *J. A. M. A.* 133: 675, 1947.
3. Miller, J. L., Slatkin, M. H., and Johnson, B. A.: Evaluation of Bacitracin in Local Treatment of Pyogenic Infections, *Arch. Dermat. and Syph.* 60: 106, 1949.



CHARLES ANDERSON ALDRICH
1898—1949

In Memoriam

CHARLES ANDERSON ALDRICH
1888-1949

CHARLES ANDERSON ALDRICH died Oct. 6, 1949, at his home in Rochester, Minn., after an extended illness. He was born at Plymouth, Mass., March 4, 1888. He received his Bachelor of Science degree from Northwestern and his Doctor of Medicine degree from the medical school of Northwestern in 1915 and interned at the Evanston Hospital and the Nursery and Children's Hospital in New York. In 1917 he started private practice and in 1921 took graduate work at Harvard in pediatrics. From 1921 to 1941 he was in active pediatric practice in Winnetka, Ill. In 1941 he retired from private practice to become chief of staff of the Children's Memorial Hospital in Chicago, where he remained until 1944 when he took over the directorship of the Rochester Child Health Project of the pediatric department of the Mayo Clinic. He was on the pediatric staff of the Evanston Hospital from the time he started practice to 1942, and was on the staff of the Children's Memorial Hospital in Chicago from 1921 until he gave up the directorship in 1944. He was a member of the teaching staff of the medical school of Northwestern from 1921 to 1944 and received his professorship in 1935. While in Winnetka he was active in community life and was on the Board of Education and a trustee of the North Shore Country Day School.

He was an active member of a number of medical societies and was chairman of the Section on Pediatrics of the American Medical Association in 1930. He served on the Council of the American Pediatric Society from 1935 to 1942 and was president in 1944. He was secretary of the American Board of Pediatrics from its founding in 1932 to 1944, and was president from 1945 to 1947. He was a member of the Editorial Board of the *JOURNAL OF PEDIATRICS* from 1941 to 1947.

In his earlier years he contributed a number of scientific articles to pediatric literature, of which his studies on nephrosis are perhaps best known. His interest in later years was in correlating child development and child psychology with the problems of pediatric practice. In 1929 he published his first book, *Cultivating the Child's Appetite*. In 1938, in association with Mrs. Aldrich, *Babies Are Human Beings* was published, which deservedly has gone through many editions and is a pediatric classic. In 1941, again with Mrs. Aldrich, *Feeding Our Old Fashioned Children* was published. For the influence of these books and for his studies on child behavior, he received the "Medal" of *Parent's Magazine*, and in 1948 the Lasker Award.

Perhaps his major interest in his long and productive career in the field of pediatrics was the task in which he had been deeply engrossed up to the time of his final illness—that of organizing, directing, and planning the unique research project in child health at Rochester.

In 1916 he married Mary McCague, who was associated with him in writing his last two books. He is survived by Mrs. Aldrich and three children, Robert A. (a physician), Cynthia, and Stephen.

B. S. V.

News and Notes

The following were certified by the American Board of Pediatrics at the examination held at Brooklyn, N. Y., Oct. 21, 22, and 23, 1949.

- Dr. Jerome Seymour Beloff, 213 East Main St., Meriden, Conn.
Dr. Thomas D. Benson, 4210 St. Paul Blvd., Rochester, N. Y.
Dr. Sydney Borow, 3400 St. Vincent St., Philadelphia 24, Pa.
Dr. Philip Briscoe, 212 Prince George, Annapolis, Md.
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Dr. Robert Koenigstein, Sea View Hospital, Staten Island, N. Y.
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Dr. Alexander Randall, 133 South 36th St., Philadelphia, Pa.
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Dr. Homer R. Rich, 227 Kiesel Bldg., Ogden, Utah.
Dr. Joseph Robinson, 76 West Union St., Wilkes-Barre, Pa.
Dr. Sydney Ross, 2440 16th St., N.W., Washington 10, D. C.
Dr. John J. Ryan, 20 Faneuil Road, Waltham, Mass.
Dr. Steven Sawchuk, 3701 North Broad St., Philadelphia 40, Pa.
Dr. Charles Frederick Scholhamer, 116 Avon St., New Haven, Conn.
Dr. Frank W. Shaffer, 1451 DeKalb St., Norristown, Pa.
Dr. Robert Traill Shipman, 907 Summit Ave., Jersey City 7, N. J.
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Dr. S. Harvey Sklar, 647 Anderson Ave., Cliffside Park, N. J.
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Dr. Ralph S. Stillier, 1633 Ripon Pl., Alexandria, Va.
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Dr. Edward Sydney Szelewa, 87 Stuyvesant Ave., Newark, N. J.
Dr. Henry C. Thacher, 11 Turner St., Auburn, Me.
Dr. Charles Varga, 303 East 20th St., New York 3, N. Y.
Dr. John T. Walke, 303 Washington, S.W., Roanoke, Va.
Dr. Alvah Marvin Weiss, 953 Paulding St., Peekskill, N. Y.
Dr. William Hoge Wood, Jr., 308 E. Market St., Charlottesville, Va.

The American Academy for Cerebral Palsy announces that its annual meeting will be held in New York City at the Waldorf-Astoria Hotel on Friday and Saturday, Feb. 17 and 18, 1950, immediately following the meeting of the American Academy of Orthopaedics.

Scientific sessions will be open to visiting orthopedic men and any other physicians interested in the problem of cerebral palsy. These sessions will be on Friday, February 17, from 2 to 5 P.M., and on Saturday morning, February 18, from 9 A.M. to 12 noon. All phases of cerebral palsy will be discussed.

University of California Medical School is offering graduate and postgraduate courses in 1950 at the Medical Center in San Francisco. Postgraduate courses on Special Problems in Pediatrics will be held February 6 through February 10.

Five authorities in specialized fields of maternal or child health have been appointed part-time consultants to the Division of Health Services of the Children's Bureau. While continuing their present positions, they will, from time to time, work with state health officers as requests are directed to the Children's Bureau. The consultants are as follows: Dr. Harry H. Gordon, Denver, for consultation on programs for premature infants; Dr. William G. Hardy, Baltimore, for hearing and speech problems; Dr. Meyer A. Perlstein, Chicago, for problems in the field of cerebral palsy; Dr. Grete L. Bibring, Boston, in developing maternal and child health programs; Dr. John Whitridge, Jr., Baltimore, for obstetric services, particularly in rural areas.

A written examination of the American Board of Pediatrics will be held in various cities on Jan. 12, 1950.

A series of Laboratory Training Courses will be given from January through the year 1950 by the Communicable Disease Center of the Public Health Service, Atlanta, Ga. The courses will vary from one to three weeks in length and over twenty courses will be given. Full details can be obtained from the Chief, Laboratory Division, Communicable Disease Center, 291 Peachtree St., N.E., Atlanta, Ga.

The International and Fourth American Congress on Obstetrics and Gynecology will be held at Hotel Statler in New York on May 14 to 19, 1950. Dr. Howard C. Taylor, Jr., of New York, is chairman of the Program Committee. Details regarding the meeting can be obtained through Dr. Fred L. Adair, 161 East Erie St., Chicago 11, Ill.

Book Reviews

New Gould Medical Dictionary. Edited by Harold W. Jones, M.D., Normand L. Hoerr, M.D., and Arthur Osol, Ph.D., Philadelphia, 1949, The Blakiston Company, 1,294 pages. Price \$8.50 (thin paper edition, \$10.75).

This is a completely new reference book in which the editors were assisted by 100 contributors, in large part from the Western Reserve Medical School, covering all the various subfields of medical specialties. A new system of pronunciation is used by syllable and accent and the principle followed of recording pronunciation in actual current use. The type is clear and easy to read. The biographic entries are far from satisfactory as, for example, Abraham Jacobi has been omitted while many names of much less importance are included. Recent pediatric literature has been somewhat overlooked. For example,

under "test" we find no mention of "Coombs test," and under the heading of "solutions" no reference to "Hartmann's solution" which has been in common use for a number of years.

A Boy Grows Up. Harry C. McKown, New York, 1949, McGraw-Hill Book Company, Inc., 312 pages Price \$2.40.

This book, written by an educator, is full of advice, rules, and inspiration for the adolescent boy. Unfortunately this approach to the problems of growing up has been tried and found wanting (even Horatio Alger has lost his appeal). There is a place for this kind of approach but it should be coupled with a deeper appreciation of the feelings and emotional problems of the adolescent. This book nowhere approaches such an understanding and would certainly not conform to our present-day concept of "guidance."

WARSON.

A Child's Eyes. Richard G. Scobee, M.D., St. Louis, 1949, The C. V. Mosby Co., 109 pages. Price \$2.00.

This small volume is a discussion of vision and the eyes of the young child with particular reference to crossed eyes, their causes, types, and treatment. As the author states in the foreword, it is written primarily for parents, and hence a pediatrician was selected for the review. It is far too complex and technically written to help any but a most highly educated parent in understanding the background and treatment of crossing. On the other hand, it is of interest to, and should be of great help to physicians and pediatricians in understanding vision in young children. The reviewer, for example, gained a much better understanding of the subject than he had held before, and for this reason it can be recommended to the practicing doctor whose knowledge of optics is likely to be rather sketchy. As to its technical accuracy, the reviewer was assured by two well-known ophthalmologists that the text is sound.

Illustrated Handbook of Simple Nursing. Wava McCullough, assisted by Marjorie Moffit, R.N., New York, 1949, McGraw-Hill Book Company, Inc., 239 pages. Price \$3.00, 20 per cent discount to teachers and schools.

This is one of the most interesting, unique, and practical books that has reached this reviewer's desk. The author during the war was on the staff of the United States Office of Education and was assigned to study the methods used in training attendant nurses, and this text for the instruction of beginners is the result. It differs from all others in that it utilizes the visual method of instruction which came into such prominence during the war when large numbers had to be rapidly trained in skills. Each task that the nurse has to carry out is illustrated by clever drawings by the author which visualize the point of the accompanying text. There are ten chapters, of which the first three deal with the care and comfort of the patient. The next four take up therapeutic and medical procedures, and the last three chapters consider the convalescent, feeding, and emergencies.

While it is stated that the purpose of the book is for the instruction of nurse attendants in simple nursing procedures, in the opinion of the reviewer it will have a much greater field of usefulness. It should be of great help in training nurses aides and in home nursing courses such as those of the Red Cross, and, in addition, it is a book that will be most useful on the shelf of the home library. We are further confident that the sections on the care of the patient could be read with profit by a large majority of the graduate nurses we have worked with over the years. It is a book on nursing with which the practicing physician should be familiar and one we intend to recommend to mothers.

B. S. V.

Editor's Column

"ANDY" ALDRICH

ON another page of this issue are the abbreviated biographic data of the active and useful life of one of the finest leaders in the development of modern pediatrics. To have known and been associated with Andy Aldrich, with his keen mind, his gentleness, his tolerance, his sense of responsibility to his patients and to his colleagues, was a privilege, as many will testify. He had the inquiring mind of the true scientist. In his earlier years, in spite of the demands of a busy practice, he found time to make careful clinical studies which would have been a credit to any "full-time" research department. His unique contribution, however, was the questioning of the problems of growth and development which arose in the routine of his everyday practice, and their solution. His philosophy, based on his experience in practice, was that "attitudes" on the part of parents in their relationships with their children are more important than "details," which was the basis of most pediatric thought some twenty years ago. This philosophy and his attitude to those under his care was well expressed in the title of his most important book, *Babies Are Human Beings*. In addition, he found time to take an active part in the life of the community in which he lived and to contribute much to its welfare. Only those of us who were associated with him in the early days of the "Board" know how much he was interested in and gave to the development of the younger man in pediatrics. He was an outstanding example of the maxim—that if you want something done, select the busy man. We believe that the historical perspective of future years will look upon him as having been one of the outstanding influences on the pediatric thought and practice of his generation.

To the younger pediatricians who subconsciously must have some ideal to pattern themselves after, his life, his work, and his medical accomplishments offer a goal well worthy of emulation.

Andy Aldrich will be greatly missed by his many friends in the pediatric world.

AUREOMYCIN IN PANCREATIC FIBROSIS

SATISFACTORY results from the use of aureomycin in the treatment of pulmonary involvement in pancreatic fibrosis have recently been reported by Schwachman and his co-workers* from the Children's Medical Center in Boston. In a series of thirty-five cases treated from two to four and one-half months, the response was excellent in thirty-one. The cough disappeared and there was a gain in appetite and body weight. The dosage used was from 20 to 30 mg. per kilogram of body weight in divided or single daily doses. Relapses, however, almost invariably occurred when the drug was discontinued.

*Schwachman, Crocker, Foley, and Patterson; *Aureomycin Therapy in the Pulmonary Involvement of Pancreatic Fibrosis*, New England J. Med. 241: 185, 1949.

One of the most interesting observations was that nausea and vomiting were rarely encountered in the patients, and that there was a decided change in the character of the stools accompanied by gain in body weight. About one-half of the patients in the series were under 2 years of age. In a recent report on a series of 134 cases of pancreatic fibrosis in THE JOURNAL by May and Lowe,* the authors reported the clinical impression that the pulmonary involvement in pancreatic fibrosis had its inception shortly after birth and reached its intensity between 6 and 18 months of age. Further, that in children surviving this period, the intensity seemed to subside, and that children living 5 to 8 years are often almost free of pulmonary complaints. Aerosol antibiotic therapy, which has been used recently for the pulmonary lesions, is a difficult and far from satisfactory method of treatment in infants and young children. Hence the experience of the Boston group with orally administered aureomycin seemingly offers a decided advance in the therapy of the condition.

1949. *May and Lowe: Fibrosis of the Pancreas in Infants and Children, J. PEDIAT. 31: 663.

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A MONTHLY JOURNAL DEVOTED TO THE PROBLEMS AND
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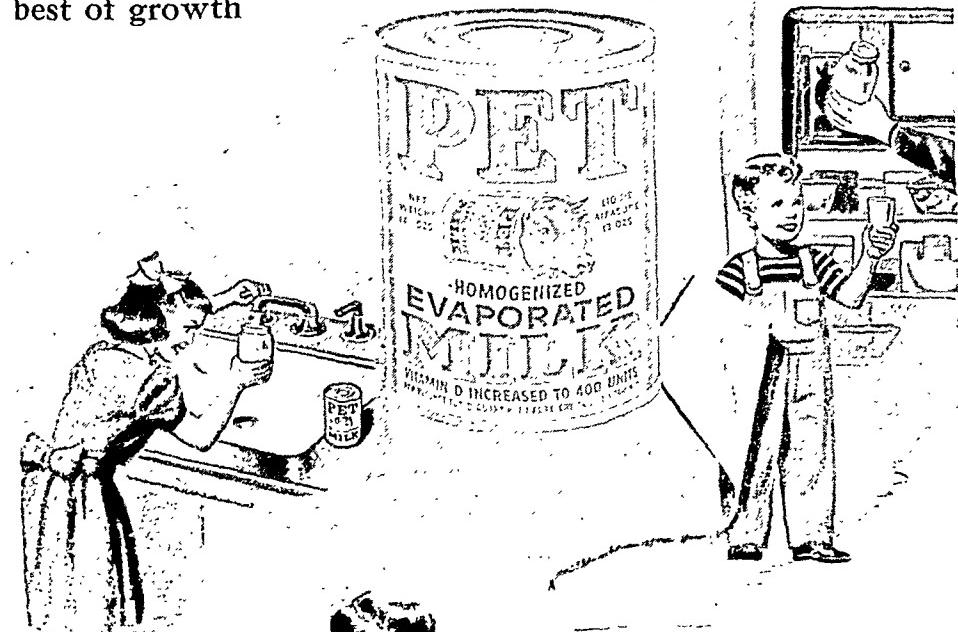
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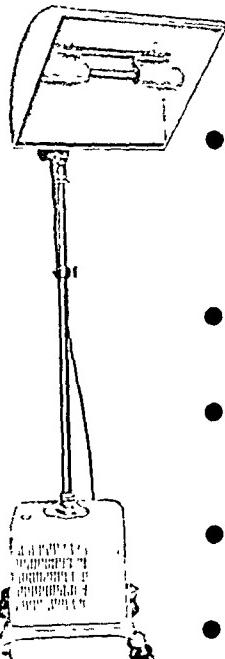
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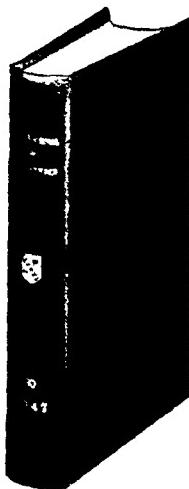
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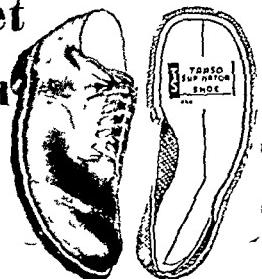
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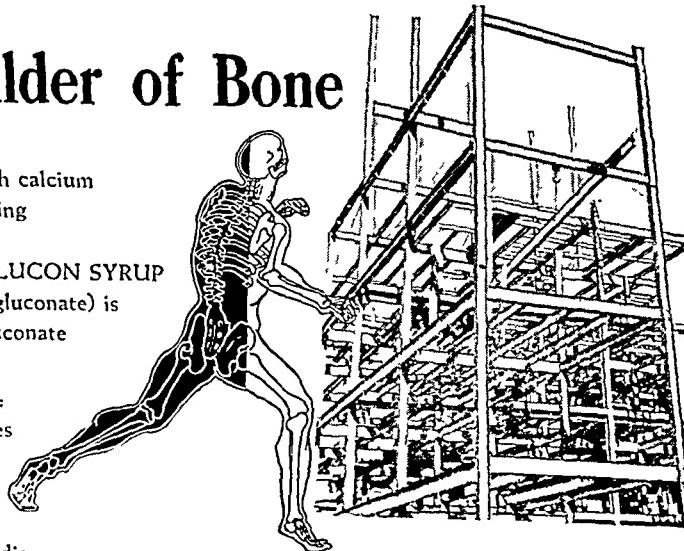
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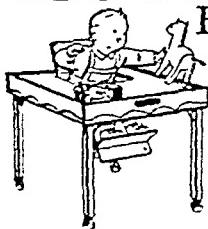
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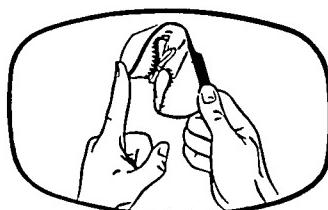
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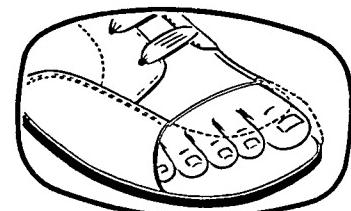
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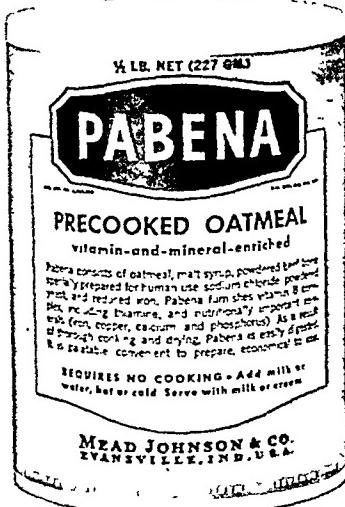
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An Old Pewter Nursing Nipple



of Sainted Memory

but Not Sanitary

ATTRACTED by a reference to "The Mead Johnson Collection of Ancient Nursing Bottles," a medical friend sent in to us as a loan the interesting pewter nipple shown above. The nipple had been given to the physician by an elderly patient who had used it as a child in the 1840's. It had also been used by her mother, her grandmother, and other members of her family.

In the eighteenth century, feeding bottles too, were made of pewter, which is an alloy of about 80 per cent tin, with copper and lead or antimony. In the wealthier homes, feeding bottles and nipples were made of a special kind of pewter called Britannia metal, which contained tin, antimony and copper, and sometimes zinc. It was more easily fashioned on the lathe and could be nickel-plated or silver-plated. Those were

the days before bacteriology, and when one examines the long, narrow, inaccessible channel in this pewter nipple through which the infant sucked his feeding, and sees that the channel could not possibly be kept clean, one wonders that the infant mortality rate of those presanitation days was not even higher.

Nowadays, babies' bottles and nipples are easily cleansed and sterilized. Certified cow's milk contains a permitted maximum of only 10,000 bacteria per cubic centimeter. Dextri-Maltose,* the carbohydrate of choice of so many physicians, is practically sterile. Rigid control methods at the dairy and in the Mead Johnson Manufacturing Department, and care in the home combine to give modern babies sanitary protection not enjoyed by those babies that were fed through pewter nipples of sainted memory.

It is significant to reflect that it was through the efforts of physicians that safe, pure milk and sanitary dairy control came to be standardized and practised, and that Dextri-Maltose came into existence in response to the widespread demand of physicians for a carbohydrate that would give superior results in infant feeding.*



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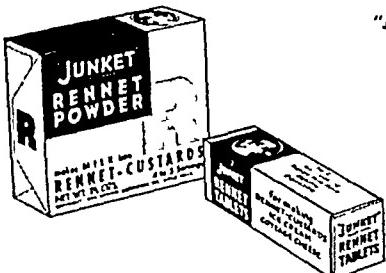
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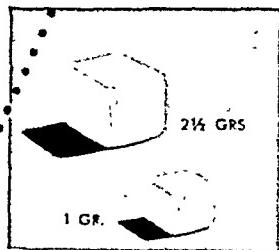


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BIBLIOGRAPHY:

- (1) Harrell, R.F.: J. Nutrition 31:283 (Mar.) 1946.
- (2) National Research Council, Recommended Dietary Allowances, 1945.
- (3) McClester, J.S.: Nutrition and Diet in Health and Disease, ed.4. Phila., W.B.Saunders Co., 1943, p.78.
- (4) Sherman, H. C.: Chemistry of Food and Nutrition, ed. 2, N.Y., Macmillan Co., 1946.
- (5) Council on Pharmacy and Chemistry and Council on Foods of the A.M.A.: The Vitamins, Chicago, American Medical Association, 1939.
- (6) Dickson, M. A.: Yearbook of Agriculture, U.S. Gov't Printing Office, Supt. of Documents, Washington, D. C., 1939, p. 203.
- (7) Elvehjem, C. A.; Siemers, A., and Mendenhall, D.R.: Am. J. Dis. Child. 50:28 (July) 1935.
- (8) Cason, J.F.: J. Pediat. 4:614 (May) 1934.
- (9) Urbach, C.; Mack, P.B., and Stokes, J., Jr.: Pediatrics 1:70 (Jan.) 1948.
- (10) Joslin, C. L., and Helms, S. T.: Arch. Pediat. 54:547 (Sept.) 1937.



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¹Von Reuss, A.: Wien. Med. Wchnschr., V. 88, p. 1023, 1938

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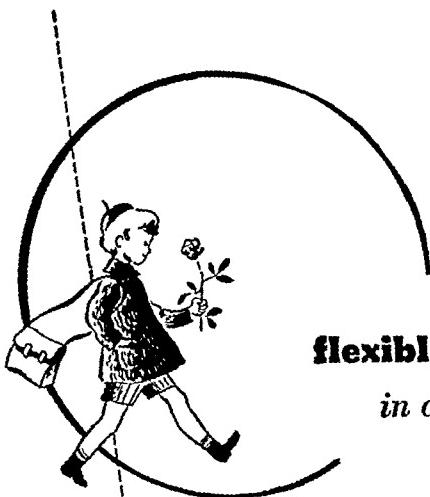


Bibliography on use of breast shields

- 1 Abramson, M. Breast Feeding the Newborn, Gen Practice Clinics, (Oct.) 1947, p. 318
- 2 McKenzie, C. H. The Use of Plastic Nipple Shields for the Lactating Breast, Journal Lancet, 65 199 (Mar.) 1948
- 3 Hoeffert, F. Simplified Breast Care, The Amer. J. Nurs., 48 372-373 (June) 1948
- 4 Thomas, E. C. The Prevention of Mastitis; the nursing problem, Edinburgh, M. J. 54 456-481, 1937
- 5 DeLee, J. B. Principles and Practice of Obstetrics, W. B. Saunders Co., Phila., 1938.

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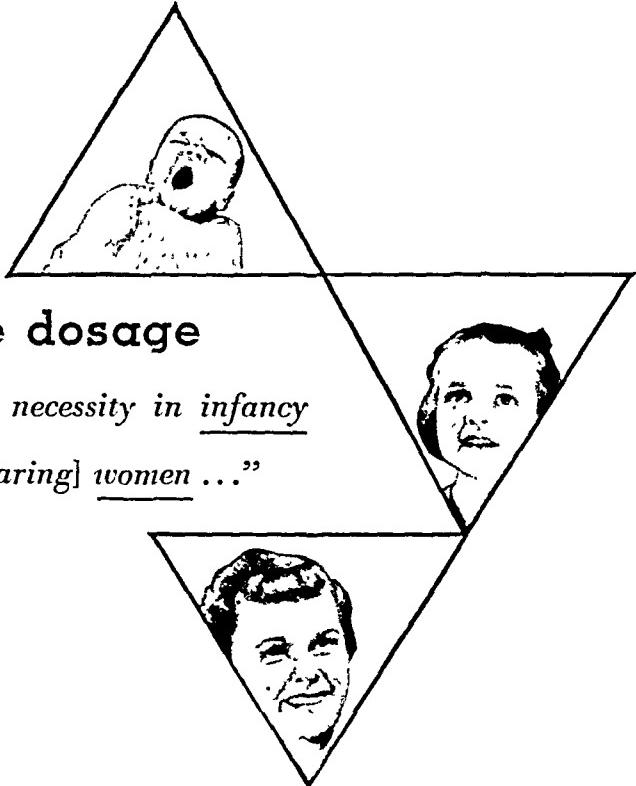
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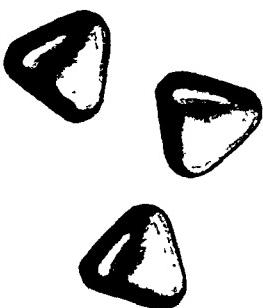
Sundaram, S. K.: Lancet. 1:568, 1948

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1. Dieckmann, W. J., and Priddle, H. D.: Am. J. Obstet. & Gynec. 57:541 (March) 1949.
2. Chesley, R. F., and Annitto, J. E.: Bull. Margaret Hague Maternity Hosp. 1:68 (Sept.) 1948.
3. Healy, J. C.: Journal-Lancet 66:218-221 (July) 1946.
4. Talso, P. J.: J. Ins. Med. 4:31-34 (Dec.-Jan.-Feb.) 1948-1949.

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(1) Reznikoff, P., and Goebel, W. F.: *Jour. Clin. Investigation*, 16:547, July, 1937. (2) Teeter, E. J.: *J.A.M.A.*, 127:973, Apr. 14, 1945. (3) Tompsett, S. L.: *Biochem. Jour.*, 34:959, June, 1940.

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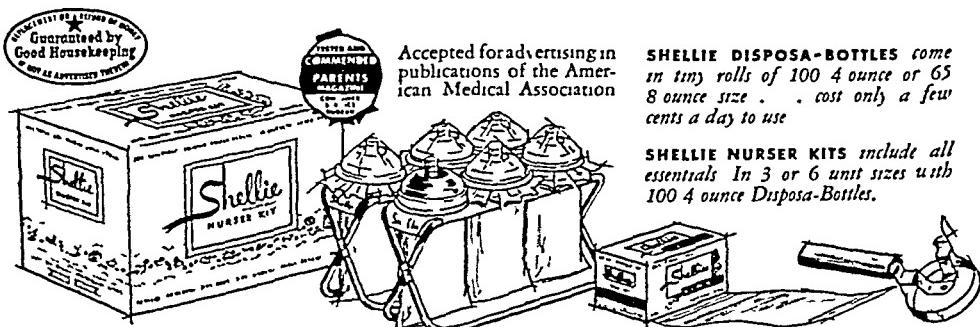
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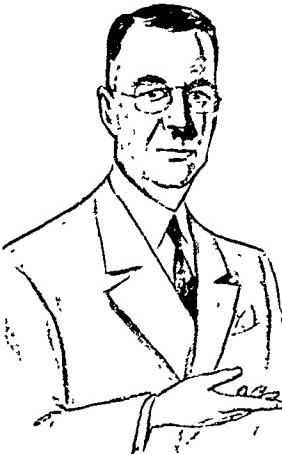
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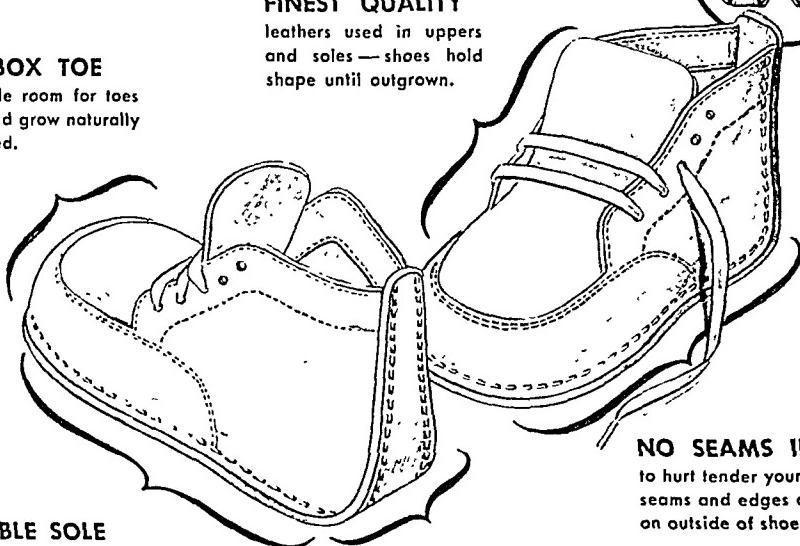
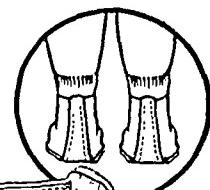
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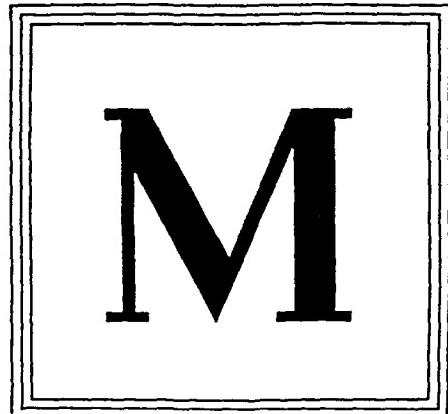
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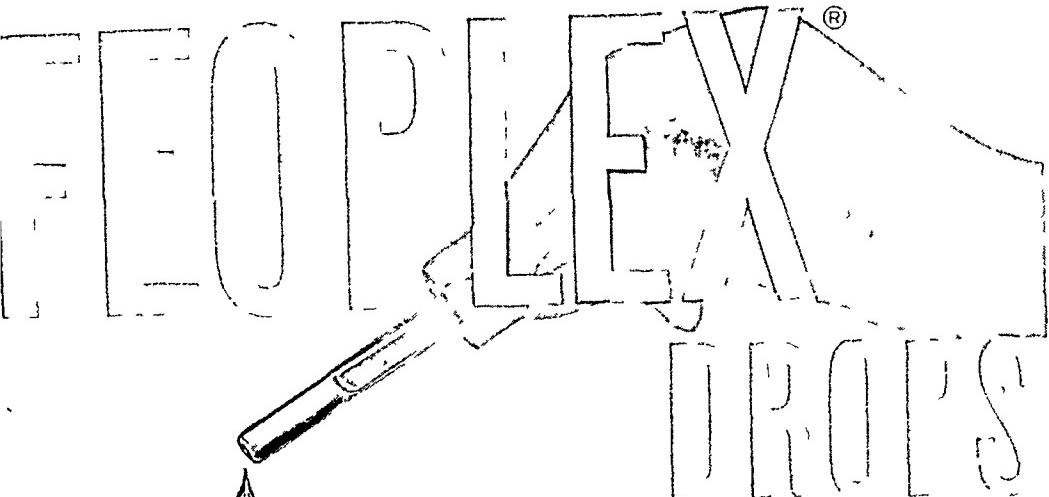
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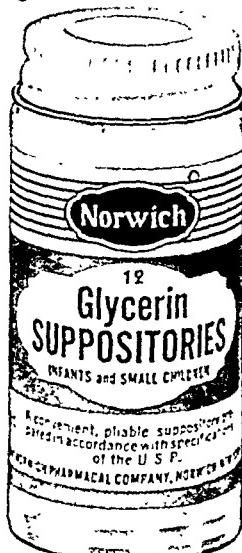
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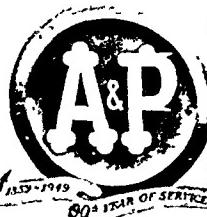
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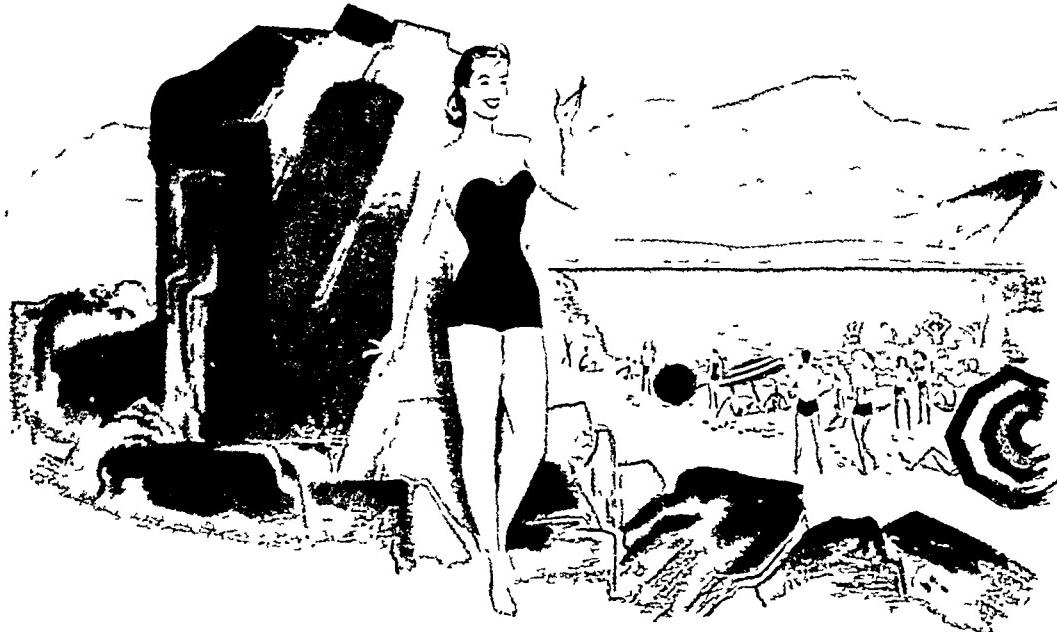
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- 2 Niedelman, M. L. Treatment of Common Skin Diseases in Infants and Children, *J. Pediat.* 32:566 (May) 1948
- 3 Cannon A. B., and McRae, M. L. Treatment of Scabies, *J. A. M. A.* 138:557 (Oct 23) 1918
- 4 Goldman L., and Feldman, M. D. Human Infestation with Scabies of Monkeys, *Arch. Dermat. & Syph.* 59:173 (Feb.) 1949
- 5 Fox E. C., and Shields T. L. Resume of Skin Diseases Most Commonly Seen in General Practice, *J. A. M. A.* 150:763 (July 2) 1949

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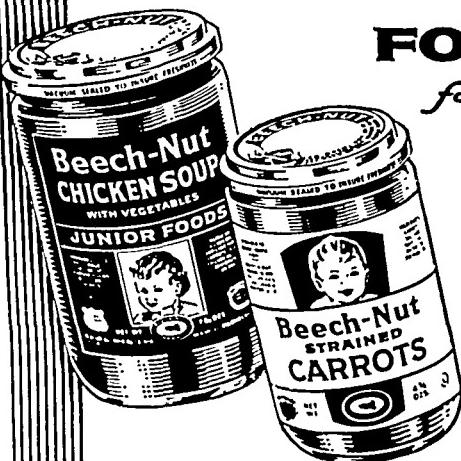
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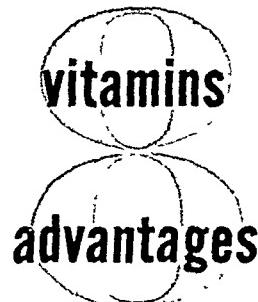
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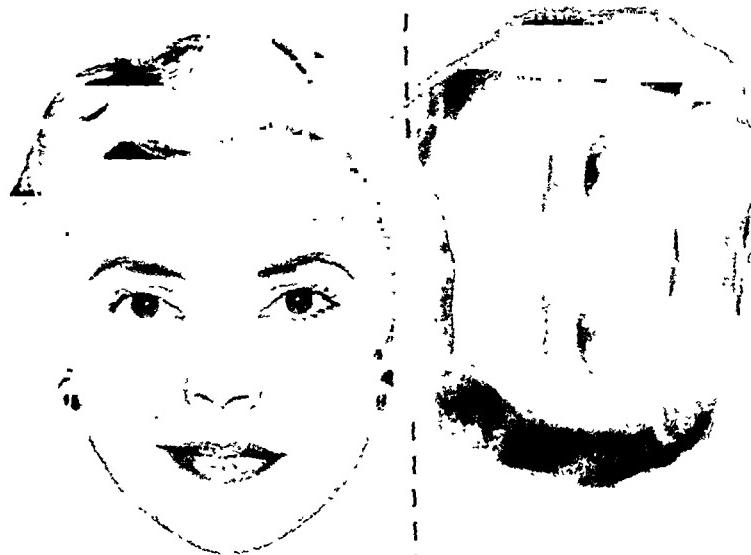
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1-Merrel, F. R. Ann. Allergy, 3397, 1947.

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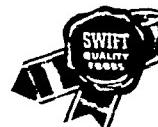
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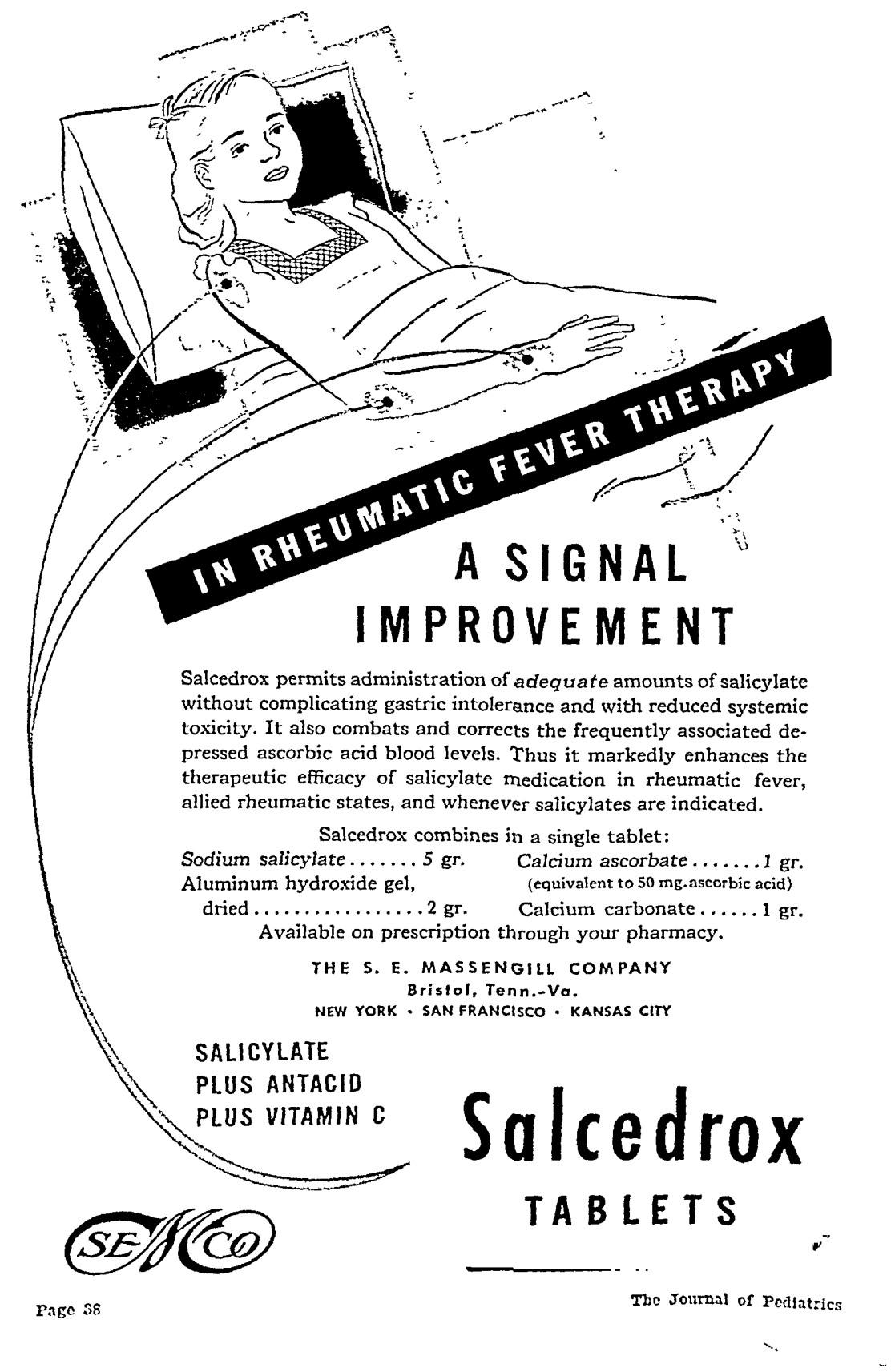
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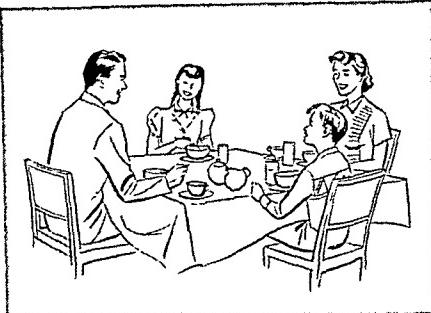
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A recent carefully controlled study at the Departments of Physiology and Nutrition of a prominent medical college on the physiologic effects of various breakfast practices shows that habitual breakfast adequacy induces positive physiologic benefits which are objectively revealed by augmented maximum work output at the pre-noon hour. Conversely, the continued omission of breakfast or the taking of coffee only induces physiologic effects leading to a significantly lower maximum work output.

In the light of these findings and to the extent indicated, breakfast adequacy may be said to definitely contribute to physiologic efficiency for greater work accomplishments during the last forenoon hour.

An 800 calorie breakfast, a 400 calorie breakfast, coffee only, and no breakfast during three-week periods constituted the breakfast practices. After habituation to each of the breakfast practices, the maximum work output of six graduate women students, determined by the bicycle ergometer at pre-noon hours, provided the data which when carefully collated justified the following conclusions:

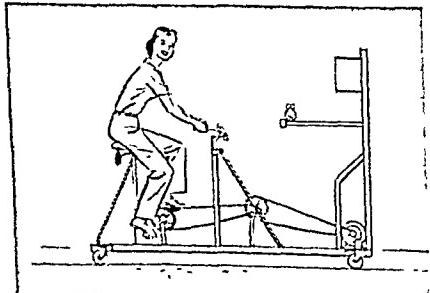
1. When "no breakfast" was the morning practice, maximum work output showed a significant *decrease* at the pre-noon hour.



2. Habituation to coffee only induced a similar *decrease* in maximum work output.
3. When habituation to the 400 calorie breakfast was attained after the coffee only period, a significant *increase* over the findings in the coffee only period in maximum work output resulted.

The conditions of the study did not permit a direct comparison of the effects of the heavy and light breakfasts on maximum work output.

For the first time, this scientific investigation gives *direct experimental* support to the recommendation long advanced by nutrition authorities for eating a breakfast which provides from one-fourth to one-third of the daily nutrient and caloric needs. A good base on which to plan an adequate breakfast is the basic breakfast pattern consisting of fruit or fruit juice, cereal, milk, bread and butter. Although the investigators do not so state, the results of the study strongly imply that maximum work output in the late morning should be increased when faulty breakfast practices are replaced by the eating of better breakfasts.



The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

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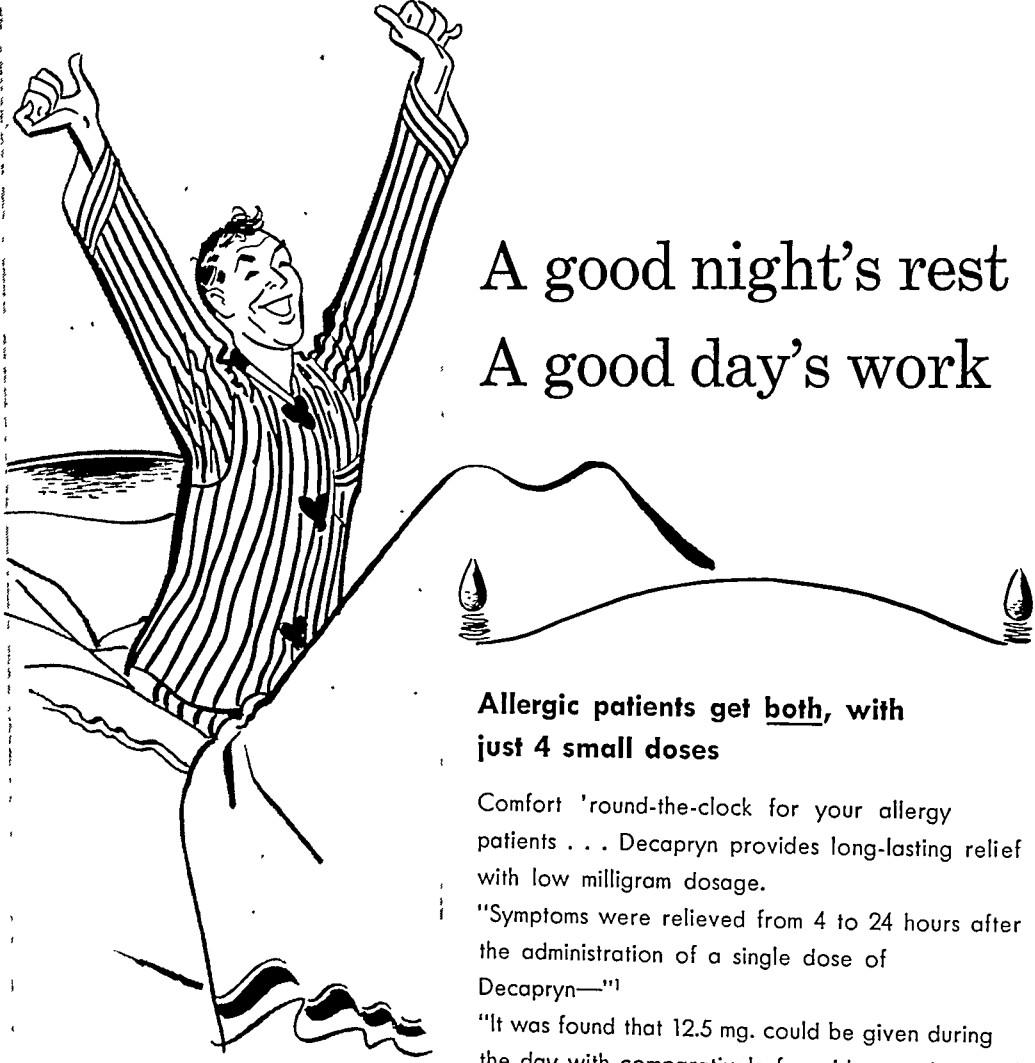
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1. Sheldon, J. M. et al Univ. Mich. Hosp. Bull. 14 13-15 (1948). 2. MacQuiddy, E. L.: Neb. State M. J. 34 123 (1949)

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* Vital Statistics—Special Reports Vol 25, No 12, National Office of Vital Statistics Washington, D C (Oct 15) 1946, p 206

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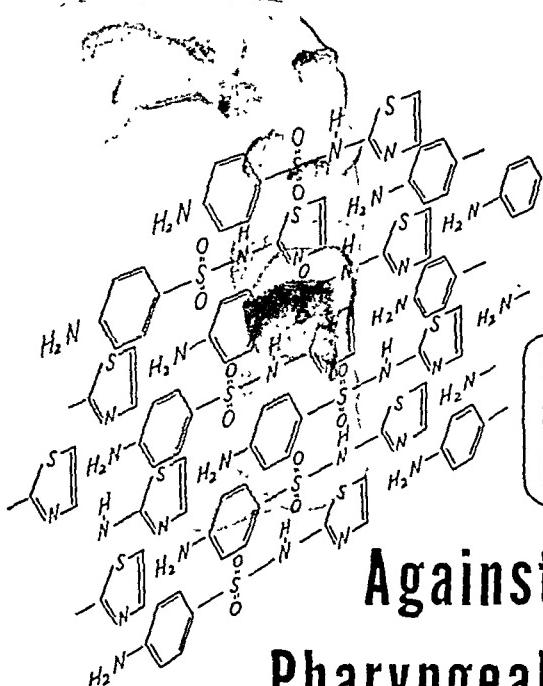


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August, 1949

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C hemoprophylaxis Against Pharyngeal Infections

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*Neiman, I. S. Prophylactic Value of Sulfathiazole,
Archives of Otolaryng. 47: 158-164 (Feb.) 1948.

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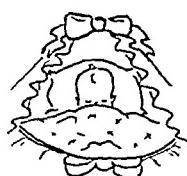
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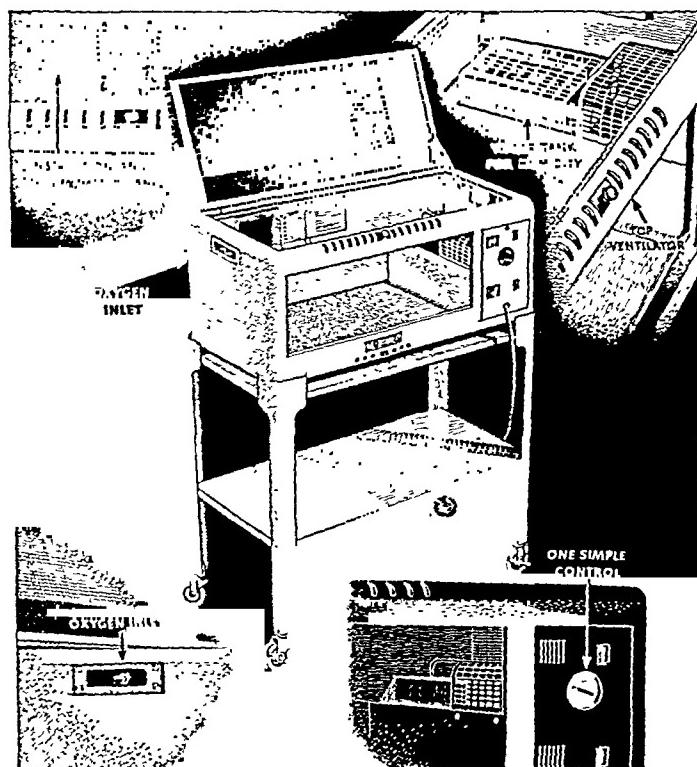
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Original Communications

ORAL PENICILLIN FOR CHILDREN WITH RHEUMATIC FEVER

JESSE W. HOFER, PH.D., M.D.

CHICAGO, ILL.

THIS study was undertaken to determine whether oral penicillin under the conditions described in this report is effective in the prevention of Lancefield Group A hemolytic streptococcal upper respiratory infections and in the elimination of throat carriers in children. The majority of the patients were actively and chronically ill with rheumatic fever and rheumatic heart disease.

Early studies^{1, 2} indicated that oral penicillin in doses similar to those employed in parenteral injections yielded inadequate blood plasma levels with small amounts excreted in the urine. Gastric acidity and reduced pH were considered to be responsible factors for its destruction. Therefore, many preparations of penicillin with antacids, buffers, capsules, oils, and waxes were introduced and studied.

When 100,000 units of penicillin were given on a fasting stomach³ the urinary excretion level was of the same order of magnitude or larger than the urinary excretion level following parenteral injections of 20,000 units. Gastric acidity⁴ is probably not a major factor in the destruction of orally administered penicillin. However, it is generally agreed that food in the stomach and active gastric digestion markedly reduces the effective absorption of this antibiotic.⁵

The efficacy of orally administered penicillin in the treatment of acute infections produced by penicillin-susceptible organisms is now established. Many authors⁶⁻¹⁰ agree that if oral doses of 100,000 units given every three hours are employed for adults, effective plasma penicillin levels can be achieved comparable with those obtained with intramuscular injections of 20,000 units every three hours. Hoffman and associates¹¹ administered crystalline potassium penicillin in the treatment of acute respiratory infections in children. Their results indicate that a satisfactory therapeutic plasma penicillin concentration can be maintained when 3,000 units per kilogram are administered every three hours.

Numerous medical authorities have noted the relationship of the Lancefield group A hemolytic streptococcus in the genesis of rheumatic fever. Coburn¹² and others have directed attention to this pathogen as the agent capable, at times, of inciting rheumatic fever. The evidence favoring Coburn's observations prompted Paul¹³ to suggest that rheumatic fever be considered one of the special or peculiar manifestations of a hemolytic streptococcal infection.

From the La Rabida Jackson Park Sanitarium, Chicago.

Abundant evidence favoring an undefined relationship between the hemolytic streptococcus and rheumatic fever is now available. The portal of entry is generally assumed to be the upper respiratory tract.¹⁴ Numerous recorded observations indicate that upper respiratory tract infections caused by a Lancefield Group A hemolytic streptococcus may initiate a train of reactions in the host resulting in a clinical state and specific lesions characteristic of the disease. The seasonal occurrence of rheumatic fever at the time of year when hemolytic streptococcal infections are prevalent, the association of epidemics of rheumatic fever following certain epidemics of hemolytic streptococcal upper respiratory infection, the appearance of definite immune responses in rheumatic fever which are characteristic of invasion of the tissues by hemolytic streptococci, and the reduction of the incidence of recurrent attacks through the prophylactic use of the sulfonamides¹⁵ lends further support to the view that these organisms are etiologic factors in the pathogenesis of rheumatic fever.

PLAN OF STUDY

Oral penicillin, crystalline G^r was administered over a seven-month period to sixty-three hospitalized children (census 45-50). Their ages ranged from 4 to 13 years, the average being 8.7 years. Most of these were chronically ill with varying degrees of active rheumatic fever or active rheumatic carditis. Each child received 200,000 units of penicillin daily in equally divided doses. One hundred thousand units were given one-half hour before breakfast and 100,000 units were given one-half hour before supper. The penicillin tablets were buffered with calcium carbonate and, in most cases, variously flavored and sweetened to improve their palatability. These were consumed like candy.

Initially one-half of the patient census was chosen for penicillin prophylaxis by blindfold selection; thereafter, alternate admissions were given oral penicillin. An equivalent group served as controls and these were given placebos appearing and tasting like the flavored and buffered medication. The control patients were equally distributed among those receiving penicillin to challenge the efficacy of penicillin prophylaxis. Their age range was from 4 to 13 years with an average of 8.9 years.

METHOD

Admission throat and gingival swabs were cultured on a solid medium containing Bacto blood agar base (Difeo) plus 5 per cent defibrinated sheep's blood. These plates were incubated aerobically at 37° C. for twenty to twenty-four hours. The above procedure was repeated on all patients and throat cultures on all personnel were conducted at weekly intervals and specifically as requested by members of the medical attending staff. Such specific requests were dependent upon the clinical symptoms or findings suggesting the presence of an upper respiratory infection of streptococcal origin.

Positive blood agar cultures were classified from 1 plus to 4 plus according to the number of hemolytic streptococcal colonies appearing on the medium. Definite and suspicious beta hemolytic strains were isolated and inoculated onto a

*The penicillin tablets used in this study were buffered with calcium carbonate, some unflavored and some flavored (Confets). These were generously supplied by the Schenley Laboratories, Inc., N. Y.

second blood agar medium and incubated for eighteen to twenty hours. Colonies producing beta hemolysis were examined microscopically. An inoculum of a confirmed beta hemolytic streptococcal colony was transferred to a large centrifuge tube containing 40 ml. sterile tryptose phosphate broth (Difeo) plus 1 per cent sterile horse serum (Lederle) and incubated for eighteen hours. The centrifuged sediment was digested and an extract was prepared according to the method of Lancefield.¹⁶ Small bore glass tubing with an outer diameter of 4 mm. was cut into 3.5 to 4 cm. lengths and one end was sealed. Into such tubes lined erect in plasticine spread on a wooden block a small amount of prepared extract was layered over Lancefield Group A antistreptococcal serum (Lederle). A positive precipitin reaction was indicated by the formation of a definite, cloudy, white ring at the junction of the extract and the serum. These tubes were incubated for thirty minutes and re-examined.

Samples of blood for the determination of penicillin levels were drawn routinely one hour and three hours after the ingestion of the antibiotic. Estimation of plasma penicillin levels was conducted with the Rammelkamp¹⁷ serial dilution method employing C 203 strain of Group A hemolytic streptococcus as the test organism. Furthermore, the Welch^{11, 18} serial dilution method employing *Bacillus subtilis* (NRRL B-558) as the organism of standard sensitivity was also utilized. The latter is prepared from stock agar slants by incubation on a shaking machine at 30° C. for eighteen to twenty hours. Serial dilutions of a standard penicillin solution (1 unit per milliliter in sterile physiologic saline) usually produces 6 tubes with no growth. Thus an unknown plasma similarly diluted and also producing 6 clear tubes contains one unit per milliliter. The lower limit of penicillin concentration that can be detected in such a standard is 0.03 unit per milliliter. Occasionally the standard may show 7 clear tubes which allows measurement to 0.015 unit per milliliter.

To insure greater accuracy of measurement, three standard series were prepared for each day of bioassays. The results were discarded if the standards did not give consistent measurements. Blood was drawn for penicillin levels under aseptic conditions and transferred to tubes containing 0.02 Gm. sodium citrate. The plasma was separated and used for the analysis. In previously reported studies^{7, 8, 11} specific inhibitors to the growth of *Bacillus subtilis* in plasma of normal subjects could not be detected.

Penicillin-sensitivity tests were conducted upon fifty-seven strains of confirmed Group A hemolytic streptococci. Two techniques were employed. The first was a serial dilution method controlled with a stock strain of hemolytic streptococcus, C203, the sensitivity of which remained practically constant at 0.008 unit per milliliter. Penicillin G was diluted serially in brain-heart infusion broth (Difeo) in concentrations varying from 1.0 units per milliliter to 0.002 unit per milliliter. To each prepared series of dilutions was added 0.1 ml. of a 1-100 dilutions of an eighteen-hour broth culture of the organism to be tested. These were incubated at 37° C. for eighteen to twenty-four hours. The last clear tube of each series containing the least amount of penicillin which inhibits bacterial growth is regarded as indicating the penicillin sensitivity of the organism. The second technique employed the Fleming¹⁹ ditch plate method.

RESULTS

A. Classification of Patients.—Children aged 4 to 13 years afflicted with or suspected of having active rheumatic fever and/or active rheumatic heart disease were referred by private physicians and hospital clinics for management. Approximately 50 per cent were admitted directly from the home and these were segregated for one week. The diagnostic criteria of Jones²⁰ were employed to establish the clinical diagnosis, while the laboratory and clinical criteria of Taran²¹ were used to establish that the diagnosed rheumatic disease was clinically active or inactive. The term "rheumatic state" signifies rheumatic fever and/or rheumatic carditis. A clinical classification of the 127 patients follows in Table I.

TABLE I. CLINICAL CLASSIFICATION OF PATIENTS

	PENICILLIN TREATED	PLACEBO TREATED
Active rheumatic state	33	39
Inactive rheumatic state	7	7
Possible rheumatic fever	13	5
Nonrheumatic	10	13
Total	63	64

B. Results of Penicillin Prophylaxis.—Sixty-three patients received oral penicillin, 200,000 units daily in equally divided doses, over a seven-month period which represented 4,239 days of penicillin therapy. Sixty-four patients received placebos during the identical seven-month period which represented 4,573 days.

No upper respiratory infections appeared in the treated group of patients from whom a confirmed Group A hemolytic streptococcus was isolated in throat cultures. From one patient during the last week of the study a single beta hemolytic colony was identified as a member of Lancefield Group A (it did not possess increased penicillin resistance as indicated by its inability to grow in the presence of 0.008 units of penicillin G per milliliter). Thus, from a total of 630 throat cultures on sixty-three patients, a single, confirmed group A beta hemolytic streptococcal colony was isolated in only one instance. This represents one throat carrier among the treated group.

Four sporadic confirmed Group A hemolytic streptococcal upper respiratory infections (pharyngitis and/or tonsillitis) appeared among the sixty-four children receiving placebos. Identified Group A* hemolytic streptococci were recovered in the throat cultures of eleven additional patients, of whom five were admission throat carriers. Thus four active upper respiratory infections and eleven carriers of these organisms were identified among the sixty-four children. Positive isolations of Group A hemolytic streptococci were obtained in fifty-seven throat cultures from a total of 677 attempts in this untreated group.

Four patients on admission (one revealing active clinical pharyngitis and tonsillitis) whose throat cultures revealed the confirmed presence of Group A hemolytic streptococci were given prophylactic oral penicillin. Their throat cultures became negative (average 3 to 4 days) and remained so throughout the study period.

*Further serologic classification of these group A beta hemolytic streptococci into specific types was not possible because the necessary type-specific serum was unavailable.

A four-month study of gingival cultures was undertaken. No confirmed group A beta hemolytic streptococci were recovered from the gingivae.

C. Penicillin Sensitivity Studies.—Penicillin sensitivity determinations were conducted on the fifty-seven strains of Group A hemolytic streptococci isolated during the period of the study. It is evident from Table II that the majority of these strains are sensitive to 0.008 unit per milliliter penicillin G when the serial dilution method is employed. This corresponds to the penicillin sensitivity of the standard C 203 strain obtained in the majority of the titrations.

While not all the isolated strains have been completely studied by the Fleming technique, none possess greater penicillin resistance than shown in Table II.

No general increase in penicillin resistance was observed during the course of this brief study.

TABLE II. PENICILLIN SENSITIVITY OF FIFTY-SEVEN STRAINS OF GROUP A HEMOLYTIC STREPTOCOCCI

PENICILLIN SENSITIVITY (UNIT PER ML.)	NUMBER OF STRAINS
.004	4
.008	32
.015	12
.03	4

D. Comparison of the Results of the Rammelkamp and Welch Serial Dilution Methods for the Bioassay of Plasma Penicillin.—Table III shows the results of two successive blood plasma bioassays for penicillin, each conducted upon the same plasma specimen of six older children of varying age and weight. The blood was drawn one hour and three hours after the morning ingestion of 100,000 units of penicillin. It is evident from the results that a single dose of 100,000 units of buffered penicillin in a fasting state promotes a satisfactory therapeutic blood plasma penicillin level. In most instances the penicillin level remained within the therapeutic range for three hours after its ingestion.

TABLE III. COMPARISON OF THE RAMMELKAMP AND WELCH PENICILLIN BIOASSAY PROCEDURES

PATIENT	AGE	WEIGHT (KG.)	1 HOUR		3 HOURS	
			RAMMEL- KAMP (UNITS PER ML.)	WELCH (UNITS PER ML.)	RAMMEL- KAMP (UNITS PER ML.)	WELCH (UNITS PER ML.)
S.W.	9	22.7	0.5	0.25	0.03	0.06
J.H.	13	35.0	0.125	0.125	0.03	0.06
R.H.	8	21.6	0.25	0.25	0.06	0.06
R.C.	10	34.8	0.125	0.125	0.06	0.06
M.T.	10	27.4	0.125	0.25	0.03	0.06
G.B.	9	44.8	0.06	0.06	0.015	<0.03
C.K.	8	26.1	0.25	0.25	0.06	0.03
R.H.	12	46.0	0.06	0.06	<0.015	0.03
N.M.	9	25.1	0.125	0.125	0.03	0.03
W.R.	9	29.8	0.125	0.125	0.03	0.03
J.P.	10	28.5	0.125	0.125	0.015	<0.03
A.K.	10	42.5	0.06	0.03	<0.015	<0.03

The results of these and other penicillin bioassays employing both techniques on identical blood samples indicated either method satisfactory for routine plasma penicillin bioassays. Because the Welch serial dilution method appeared most suitable for routine bioassays, it was selected and employed during the latter part of the study and the Rammelkamp serial dilution method was discontinued.

DISCUSSION

For many years physicians have attempted to lessen the frequency of rheumatic recurrences by the prophylactic use of various drugs. The early studies employed salicylates between rheumatic attacks and later they were given coincident with and for about a month following an upper respiratory infection in rheumatic children.²² The salicylates, however, do not prevent recurrences by a direct chemotherapeutic effect on the hemolytic streptococcus.

The efficacy of the sulfonamides in the treatment of infections resulting from invasion of the tissues by the group A hemolytic streptococcus stimulated numerous studies in which small doses of sulfonamides were employed in the prevention of rheumatic recurrences in susceptible children. Results of sulfonamide prophylaxis as employed in civilian populations have been reviewed.¹⁵ These indicate that the drug markedly decreases the rheumatic recurrence rate.

Sulfonamide-resistant strains of Group A hemolytic streptococci appeared in the armed services of the United States during World War II.²³⁻²⁸ Although it was recognized that the civilian population was exposed to these resistant strains (mainly Types 3, 17, and 19), no epidemics therefrom were reported until 1946, when an outbreak of sulfonamide-resistant Type 19 infections appeared in Cooperstown, N. Y.²⁹ A recent report on the incidence of sulfonamide-resistant strains of Group A hemolytic streptococci isolated from actively infected patients and carriers revealed only one strain, a Type 19, in 167 isolations.³⁰

These reports indicate the infrequency of sulfonamide-resistant strains of Group A hemolytic streptococci in civilian populations. Yet a potential hazard from this source exists among individuals receiving small daily prophylactic doses of sulfonamide administered for the prevention of rheumatic fever recurrences.

From purely theoretical viewpoints, according to Hartman and Weinstein,³⁰ "these resistant bacteria could arise as naturally occurring variants; they could arise as variants of normally susceptible strains as a result of contact with and adaptation to the drug, or they could arise as spontaneous genetic mutants." Jennings and Delamater²¹ studied a scarlet fever epidemic of Group A, Type 17, sulfadiazine-resistant hemolytic streptococcus. They reported that they found evidence to suggest that the organism became resistant during the early phase of the epidemic in the face of sulfadiazine prophylaxis where small dosage produced ineffective drug levels and possibly promoted mutable organisms to develop drug resistance. In a discussion of epidemiologic problems as a result of human action Burnet³² contends that there is no reasonable doubt that the appearance of these resistant strains of streptococci was directly due to the wide-scale use of sulfadiazine as a prophylactic drug.

Penicillin-resistant strains of Lancefield Group A hemolytic streptococci would be of considerable clinical significance, but reviews of the literature have not revealed a proved instance of increased resistance associated with a human infection.³³ Employing in vitro techniques Gezon reported increases in resistance varying from no increase to a seventeen-fold increase following sixty transfers onto media containing the highest concentration of penicillin permitting growth. In those instances where heightened resistance was observed, there was noted an associated marked loss of mouse virulence, loss of group-specific precipitinogen of Lancefield, and a reduction and variation of hemolytic capacity. Employing in vivo techniques³⁴ in embryonated eggs and in mice, no alteration in penicillin sensitivity was produced. There is considerable significance to be attached to the laboratory development of increased resistance of Group A hemolytic streptococci to penicillin if proved reduction of virulence results.^{33, 35} These findings are at variance with the studies on sulfonamides where the virulence of the resistant strains remains unimpaired.^{25-29, 31}

Milzer, Kohn, and MacLean³⁶ reported a high incidence of penicillin-resistant strains of hemolytic streptococci following the oral administration of 50,000 units of penicillin twice daily to inactive rheumatic children. Unfortunately, no attempt was made to group the isolated strains by the Lancefield precipitin technique. Based upon the reported frequency of the Group A hemolytic streptococci recovered by throat cultures, they assume that at least one-half of the resistant strains belong to Group A.

Studies of Markowitz and Kuttner⁵ demonstrate that 50,000 units of penicillin administered orally to the fasting child produce serum levels varying from a maximum 0.25 unit per milliliter after one hour to 0.04 unit per milliliter after two hours. A definite bactericidal effect against standard C203 *Streptococcus pyogenes* was observed by Eagle³⁷ with a penicillin concentration of 0.006 unit per milliliter. The maximal rate of killing was obtained at a level of 0.064 unit per milliliter.

Studies³³ on 203 freshly isolated virulent strains of group A hemolytic streptococci from patients with acute upper respiratory disease, none of whom received penicillin, revealed a general lack of penicillin resistance (range from <0.01 to 0.02 unit per milliliter). Recent observations of Massell, Dow, and Jones³⁸ indicate that group A hemolytic streptococci isolated from the throats of carriers were sensitive to penicillin (range from 0.006 to 0.04 unit per milliliter). They were unable to explain why only 75 per cent of the carriers could be completely freed of the organisms when 300,000 to 1,000,000 units daily were administered for ten days. They consider the presence of tonsils to be a possible factor preventing such therapy from being 100 per cent efficient.

The present study was undertaken to evaluate the capabilities of oral penicillin in the prevention of Group A hemolytic streptococcal upper respiratory infections and the elimination of throat carriers in a children's hospital, the majority of the patients being chronically ill, rheumatic children. During the seven-month study, 8,500 doses of oral penicillin were administered. No untoward reactions of penicillin sensitivity^{39, 40} such as skin manifestations (urticaria, angioneurotic edema, etc.), glossitis, diarrhea, arthralgia, or unexplained

febrile phenomena appearing on initiation of therapy or two weeks thereafter alleviated by drug discontinuance, etc., were observed. The ease of administration of penicillin and its general acceptance in candy form by the majority of the children compares favorably with any oral medication. Routine laboratory examinations of blood and urine to detect and correct any potential toxic manifestations arising from its use were unnecessary with oral penicillin as distinguished from the potential hazard associated with the sulfonamides, even though administered in minimal dosage.⁴¹

Except for its present high cost preventing its more general use, penicillin has many advantages over the sulfonamides in protecting against Group A hemolytic streptococcal infections. From the results of this study and the results presented in the discussion penicillin possesses greater antistreptococcal capacities than the sulfonamides. It has been employed with dramatic results in therapy for sulfonamide-resistant group A hemolytic streptococcal infections.³¹ Recorded studies have not presented satisfactory evidence that penicillin-resistant group A organisms have appeared in human infections, nor has resistance been stimulated by laboratory efforts without loss of virulence.

An argument against the prophylactic use of oral penicillin may be advanced in the observation that the nonhemolytic, viridans streptococci and certain serologic groups of hemolytic streptococci other than Group A may become increasingly resistant to penicillin when such therapy is inadequate for their complete elimination. Such organisms are potentially capable, under certain circumstances, of causing bacterial endocarditis. Increasing amounts of administered penicillin would, therefore, be necessary to overcome infections resulting from bacteria possessing this induced resistance.

Oral penicillin offers considerable promise in the control of epidemics of upper respiratory infections among children in homes, schools, and other institutions.⁴² The abundant evidence favoring its employment in Group A hemolytic streptococcal upper respiratory infections, however, offers great promise in protecting chronically ill rheumatic children from infections of this type. It appears that not all strains of these pathogens are capable of inciting rheumatic recurrences,⁴³ yet many are responsible for provoking reactivations or exacerbations of the chronic, active, rheumatic state.

It must be admitted that we do not possess conclusive evidence that deep-seated foci of hemolytic streptococci may not exist in inaccessible structures such as the tonsils, paranasal sinuses, and deep lymph nodes draining the upper respiratory passages. From the results of this report the dosage of oral penicillin employed was sufficient to eliminate group A hemolytic streptococci from the readily accessible mucous membranes of the mouth and throat.

This small study, while not conclusive, indicates that oral penicillin is a most satisfactory antibiotic in preventing group A hemolytic streptococcal upper respiratory infections. Additional planned and controlled studies directed toward protecting children with rheumatic fever are indicated.

CONCLUSIONS

Oral penicillin administered in the fasting state to chronically ill rheumatic children in equally divided doses (200,000 units per day) produces a satis-

factory therapeutic blood plasma level for approximately three hours following each administration.

Sixty-three children receiving oral penicillin over a seven-month period had no confirmed Group A hemolytic streptococcal upper respiratory disease, and one child was a confirmed carrier. Sixty-four children served as controls during this period, four had confirmed Group A hemolytic streptococcal upper respiratory infections and eleven were proved carriers.

Employing two techniques for the estimation of penicillin resistance in fifty-seven strains, there was no demonstrable increase in resistance among these strains during this brief study.

The employment of oral penicillin in prophylaxis against group A hemolytic streptococcal upper respiratory infections has been compared with the present status of the sulfonamides. Present knowledge regarding penicillin resistance is briefly reviewed.

The author wishes to acknowledge with gratitude the technical assistance of Mrs. Margaret Smith and Mrs. Phyllis Reinfranck in the bacteriologic identifications, penicillin resistance studies, and the penicillin assays.

REFERENCES

1. Florey, M. D., and Florey, H. W.: General and Local Administration of Penicillin, *Lancet* 1: 387, 1943.
2. Rammelkamp, C. H., and Keefer, C. S.: Absorption, Excretion, and Distribution of Penicillin, *J. Clin. Investigation* 22: 425, 1943.
3. Free, A. H., Leonards, J. R., McCullough, D. R., and Biro, B. E.: The Urinary Excretion of Penicillin After Oral Administration to Normal Human Subjects, *Science* 100: 431, 1944.
4. McDermott, W., Bunn, P. A., Benoit, M., Dubois, R., and Reynolds, M. E.: The Absorption, Excretion, and Destruction of Orally Administered Penicillin, *J. Clin. Investigation* 25: 190, 1946.
5. Markowitz, M., and Kuttner, A. G.: A Study of the Absorption and Excretion of Oral Penicillin in Children, *J. PEDIAT.* 31: 195, 1947.
6. McDermott, W., Bunn, P. A., Benoit, M., DuBois, R., and Haynes, W.: Oral Penicillin, *Science* 101: 228, 1945.
7. Hoffman, W. S., and Volini, I. F.: Studies in the Oral Administration of Penicillin. I. Assays of Various Preparations and the Determination of the Effective Therapeutic Dose, *Am. J. M. Sc.* 213: 513, 1947.
8. Hoffman, W. S., and Volini, I. F.: Studies in the Oral Administration of Penicillin. II. Results of Treatment of Pneumococcal Lobar Pneumonia and Other Acute Infections with Several Oral Penicillin Preparations, *Am. J. M. Sc.* 213: 520, 1947.
9. Ross, S., Burke, T. G., and Olansky, S.: Oral Administration of Penicillin N. *Eng. J. Med.* 236: 817, 1947.
10. Volini, I. F., Hoffman, W., Hughes, J. R., and Peffer, J. R.: Studies in the Oral Administration of Penicillin. III. Oral Penicillin in the treatment of Pneumococcal Pneumonia, *Ill. Med. J.* 94: 235, 1948.
11. Hoffman, W. S., Hofer, J. W., and Gordon, H.: The Treatment of Acute Respiratory Infections in Children with Orally Administered, Unbuffered Penicillin Solutions, *J. PEDIAT.* 32: 1, 1948.
12. Coburn, A. F.: The Factor of Infection in the Rheumatic State, Baltimore, 1931, Williams and Wilkins Co.
13. Paul, J. R.: The Epidemiology of Rheumatic Fever and Some of its Public Health Aspects, ed. 2, Metropolitan Life Insurance Company, 1943.
14. Kerr, W. J.: Pathogenesis of Rheumatic Fever, *Ann. Int. Med.* 29: 587, 1948.
15. Rosenberg, E. F., and Hench, P. S.: Recent Advances in the Treatment of Rheumatic Fever, With Special Reference to Sulfonamide Prophylaxis and Intravenous Salicylate Therapy, *Med. Clin. N. America*, p. 489, 1946.
16. Lancefield, R.: A Serological Differentiation of Human and Other Groups of Hemolytic Streptococci, *J. Exper. Med.* 57: 571, 1933.
17. Rammelkamp, C. H.: A Method of Determining the Concentration of Penicillin in Body Fluids and Exudates, *Proc. Soc. Exper. Biol. & Med.* 51: 95, 1942.

18. Randall, W. A., Price, C. W., and Welch, H.: The Estimation of Penicillin in Body Fluids, *Science* 101: 365, 1945.
19. Fleming, A.: Proc. Roy. Soc. Med. 34: 342, 1941.
20. Jones, T. D.: The Diagnosis of Rheumatic Fever, *J.A.M.A.* 126: 481, 1944.
21. Taran, L. M.: Laboratory and Clinical Criteria of Rheumatic Carditis in Children, *J. PEDIAT.* 29: 77, 1946.
22. Schlesinger, B.: The Public Health Aspects of Heart Disease in Children, *Lancet* 1: 593, 649, 1938.
23. Navy Department, Bureau of Medicine and Surgery: The Prevention of Respiratory Tract Bacterial Infections by Sulfadiazine Prophylaxis in the United States Navy, Washington, D. C., Government Printing Office, 1944, 162 pp.
24. Coburn, A. F.: Mass Sulfadiazine Prophylaxis of Respiratory Diseases in U. S. Navy, *Bull. New York Acad. Med.* 21: 281, 1945.
25. Epidemiology Unit No. 22: Sulfadiazine (Sulfonamide) Resistant Strains of Beta Hemolytic Streptococci: Appearance During Course of Sulfadiazine Prophylaxis at Large Naval Training Center, *J.A.M.A.* 129: 921, 1945.
26. Damrosch, D. S.: Chemoprophylaxis and Sulfonamide Resistant Streptococci, *J.A.M.A.* 130: 124, 1946.
27. Delamater, E. D., Jennings, R., and Wallace, A. W.: Preliminary Report of Outbreak of Streptococcal Disease Caused by Sulfadiazine Resistant Group A, Type 17, Hemolytic Streptococcus, *J. Infect. Dis.* 78: 118, 1946.
28. Roberg, M. B.: Epidemic Caused by Sulfadiazine Resistant Strain of Streptococcus Hemolyticus (Group A Type 17), *J. Infect. Dis.* 78: 135, 1946.
29. Johnson, R. D., and Hartman, T. L.: Sulfadiazine Resistant Streptococcal Infections in Civilian Community, *J. Clin. Investigation* 26: 325, 1947.
30. Hartman, T. L., and Weinstein, L.: The Problem of Sulfonamide Resistant Hemolytic Streptococci, *N. Eng. J. Med.* 238: 560, 1948.
31. Jennings, R., and DeLamater, E. D.: Penicillin Therapy of Scarlet Fever and the Streptococcus Carrier, *Am. J. Med.* 2: 1, 1947.
32. Burnet, F. M.: Epidemiology Today, *M. J. Australia* 2: 825, 1946.
33. Gezon, H. M.: Antibiotic Studies on Beta Hemolytic Streptococci: I. Penicillin Resistance Acquired by Group A Organisms, *Proc. Soc. Exper. Biol. & Med.* 67: 208, 1948.
34. Gezon, H. M., and Collins, G. R.: Antibiotic Studies on Beta-Hemolytic Streptococci: IV. Penicillin Resistance Induced in Mice and Embryonated Eggs, *Proc. Soc. Exper. Biol. & Med.* 69: 312, 1948.
35. Rake, G., McKee, C. M., Hamre, D. M., and Houek, C. L.: Studies on Penicillin: II. Observations on Therapeutic Activity and Toxicity, *J. Immunol.* 48: 271, 1944.
36. Milzer, A., Kohn, K. T., and MacLean, H.: Oral Prophylaxis of Rheumatic Fever With Penicillin, *J. A. M. A.* 136: 536, 1948.
37. Eagle, H.: The Kinetics of the Bactericidal Action of Penicillin and the Therapeutic Significance of the Blood Penicillin Level, *J. Baet.* 54: 6, 1947.
38. Massell, B. F., Dow, J. W., and Jones, T. D.: Orally Administered Penicillin in Patients with Rheumatic Fever, *J.A.M.A.* 138: 1030, 1948.
39. Anderson, D. G., and Keefer, C. S.: The Therapeutic Value of Penicillin: A Study of 10,000 Cases, *J. E. Edwards, Ann Arbor, Mich.*, 1948.
40. Morganson, W. J.: Toxic Reactions Accompanying Penicillin Therapy, *J.A.M.A.* 132: 915, 1946.
41. Baldwin, J. S.: Sulfadiazine Prophylaxis in Children and Adolescents with Inactive Rheumatic Fever, *J. PEDIAT.* 30: 284, 1947.
42. Lapin, J. H.: Prophylaxis of Upper Respiratory Infections in Children Treated with Oral Penicillin, *J. PEDIAT.* 32: 119, 1948.
43. Kuttner, A. G., and Krumwiede, E.: Observations on the Effect of Streptococcal Upper Respiratory Infections on Rheumatic Children: A Three Year Study, *J. Clin. Investigation* 20: 273, 1941.

FURTHER STUDIES ON ORAL PENICILLIN IN THE PROPHYLAXIS OF RECURRENT RHEUMATIC FEVER

MARTIN M. MALINER, M.D., SOL DARRELL AMSTERDAM, M.D., AND
C. C. ARRECHE, M.S.
BROOKLYN, N. Y.

IN AN earlier article⁴ we discussed the theory behind the use of oral penicillin and the earlier studies using sulfonamides for the prevention of rheumatic fever. Most of these studies are predicated upon the idea that the rheumatic disease occurs shortly after an upper respiratory infection of one to three days' duration caused by particular strains of hemolytic streptococci, followed by a latent interval of one to three weeks during which some phenomenon, either allergic, immunologic, or otherwise takes place, subsequently followed by the clinical manifestations of the rheumatic infection in any of its protean forms (Hansen⁵). Holbrook⁶ found as many as 50 per cent of certain susceptible persons had a rerudescence of rheumatic fever within two to three weeks following an upper respiratory infection. Hugh Morgan,⁷ in 1943, reported that 90 per cent of youths in World War II who suffered attacks of rheumatic fever while stationed in army camps, had an immediate previous streptococcus infection with an average latent period of sixteen days before the symptoms of rheumatic fever developed. Massel, Dow, and Jones⁸ found that at some army posts actual epidemics of rheumatic fever resulted when upper respiratory infections due to hemolytic streptococci were present.

From the above reports it would seem logical to assume that any agent which would effectively eliminate streptococci from throat cultures would prevent the development of rheumatic fever.

Most of the accounts on the use of oral penicillin for the suppression of hemolytic streptococci in the throat and upper respiratory regions reported in the literature have been favorable. The majority used fairly large doses. Thus Massell, Dow, and Jones⁸ used 300,000 to 1,000,000 units daily. Ross, Burke, and Olansky⁹ used 50,000 units every three hours for six doses on adults and children were given a total of 200,000 to 500,000 units. One 11-year-old child with subacute bacterial endocarditis was given 100,000 units every three hours for fourteen days. The authors claimed that the results do not differ materially from those with parenteral administration except for the larger dose required.

In contrast to these studies, the authors published the results of a series of forty-four cases in which one-half of the patients received penicillin troches^{*} and one-half were used as controls.⁴ All gave a history of rheumatic fever and some evidence of heart disease. The dosage was at first 1,000 units three times a day (1945 to 1946) and later increased to 5,000 units three times a day in 1946 and 1947. In this series we gave the penicillin troches in order to attack

From the Department of Pediatrics, University Hospital, New York University—Bellevue Medical Center, New York.

*The troches used in the previous series as well as in this present series are marketed under the name of Lederillin Crystalline Penicillin G Troches, 5,000 units each. They were supplied by the Lederle Laboratories Division of the American Cyanamide Company, 30 Rockefeller Plaza, New York, N. Y., who also aided by a grant.

the streptococcus at the apparent source of the trouble and we found the dose sufficient to effect bacteriostasis but, nevertheless, weak enough not to produce a blood level sensitizing the patient to penicillin. No culture or penicillin determinations were taken in this series. Penicillin is preferable to sulfa drugs because the latter depend largely upon a blood level and require repeated leucocyte, hemoglobin, and differential blood counts plus urinalysis. Baldwin¹⁰ states: "Despite our good fortune in not encountering serious toxic manifestations, it is to be emphasized that such should be watched for and that a total white and polymorphonuclear count should be followed for at least the first two months of the prophylactic therapy with sulfa drugs. The urine should be followed for albumin and red cells at regular intervals throughout the treatment."

Having seen the apparent prophylactic efficacy in the preceding series, inasmuch as none of the twenty-two children receiving penicillin troches developed rheumatic fever while four of the controls receiving placebos did so, we determined to run another series with observation of throat cultures and determination of penicillin concentration in the throat and blood.

In our new series, forty-four children were selected (similar to the group in the previous study. Twenty-two received the troches and the remaining twenty-two served as controls.

TABLE I. SUMMARY OF CASES STUDIED

	AGE IN YEARS		
	4-8	8-12	12-15
Penicillin	5 cases	10 cases	7 cases
Controls	6 cases	12 cases	4 cases
CARDIAC DIAGNOSIS			
	POTENTIAL RHEUMATIC HISTORY	RHEUMATIC MITRAL DISEASE	CONGENITAL
Penicillin	5 cases	14 cases	3 cases
Controls	7 cases	12 cases	3 cases

Method Used for the Study of the Penicillin Level in the Throat and Blood.—For the determination of the penicillin level in the throat and in the blood, the procedure used was that of Cooke's published in the third edition of Levinson and MacFate's textbook on clinical diagnosis.¹¹ This method consists in diluting the serum (blood) or fluids with sterile saline and testing the sensibility of a standard *Staphylococcus aureus* culture not older than twenty-four hours.

In the case of the determination of the oral penicillin level, the bacteriologist encountered several difficulties. The first one was in devising a method of obtaining the specimen from the throat. This was solved by making the person hawk up secretions from the throat and expectorate them into a sterile Petri dish, avoiding as much as possible the saliva that accumulates in the front of the mouth. The second and more important difficulty, as far as the bacteriology was concerned, was the contamination of these secretions with all sorts of organisms at the time of expectoration. To avoid this, we used the new B.D. Swinny filter for small amounts of fluid, thus obtaining a sterile fluid for examination.

Cases Studied.—Almost all of the cases that were studied were of patients at the Children's Cardiac Clinic at the New York Post-Graduate Medical School and Hospital. Most patients gave a history of rheumatic fever. A few were congenital heart cases. While the majority showed definite cardiac lesions, a few were classed as potential cardiaques on account of the rheumatic fever history with no definite cardiac lesions thus far.

Time of Penicillin Troches in the Mouth.—The penicillin lozenges were administered one hour after meals to avoid contamination from food particles.

ORAL PENICILLIN LEVEL (5,000 UNITS)

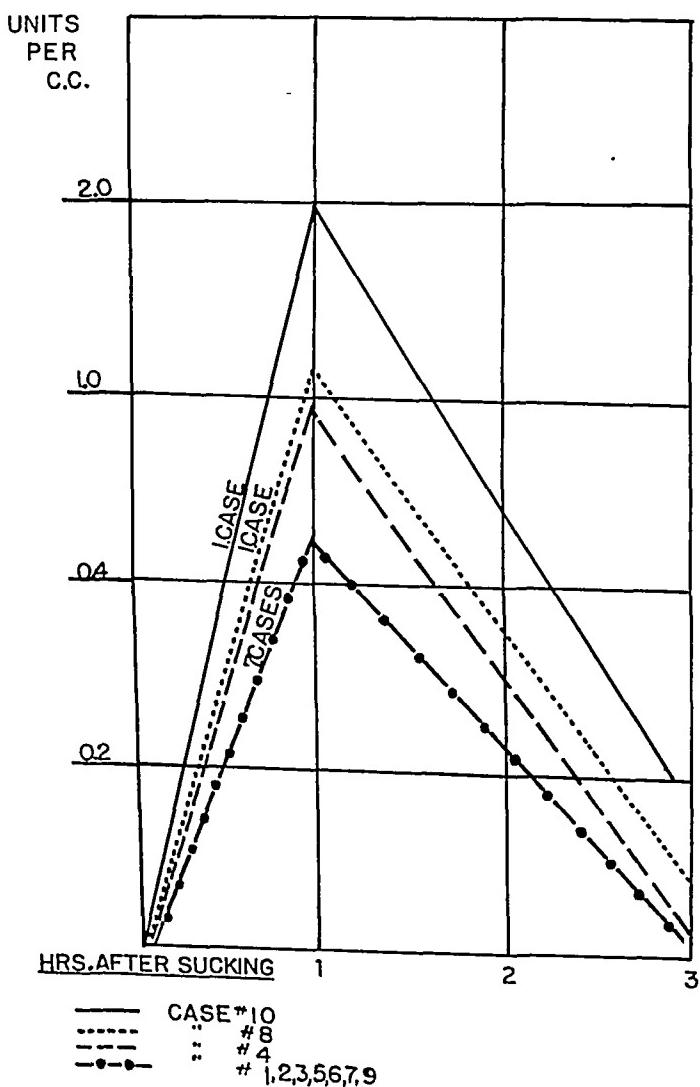


Fig. 1.

Each case was timed after the penicillin troches were administered to determine the minutes employed in sucking the troches. The longest took fourteen minutes and the shortest eight. The same time was consumed in the 5,000 units of penicillin as in the few cases receiving 10,000 units.

Penicillin Level in the Mouth.—Fig. 1 summarizes the saliva penicillin level in the cases receiving 5,000 units and Fig. 2, those upon whom 10,000

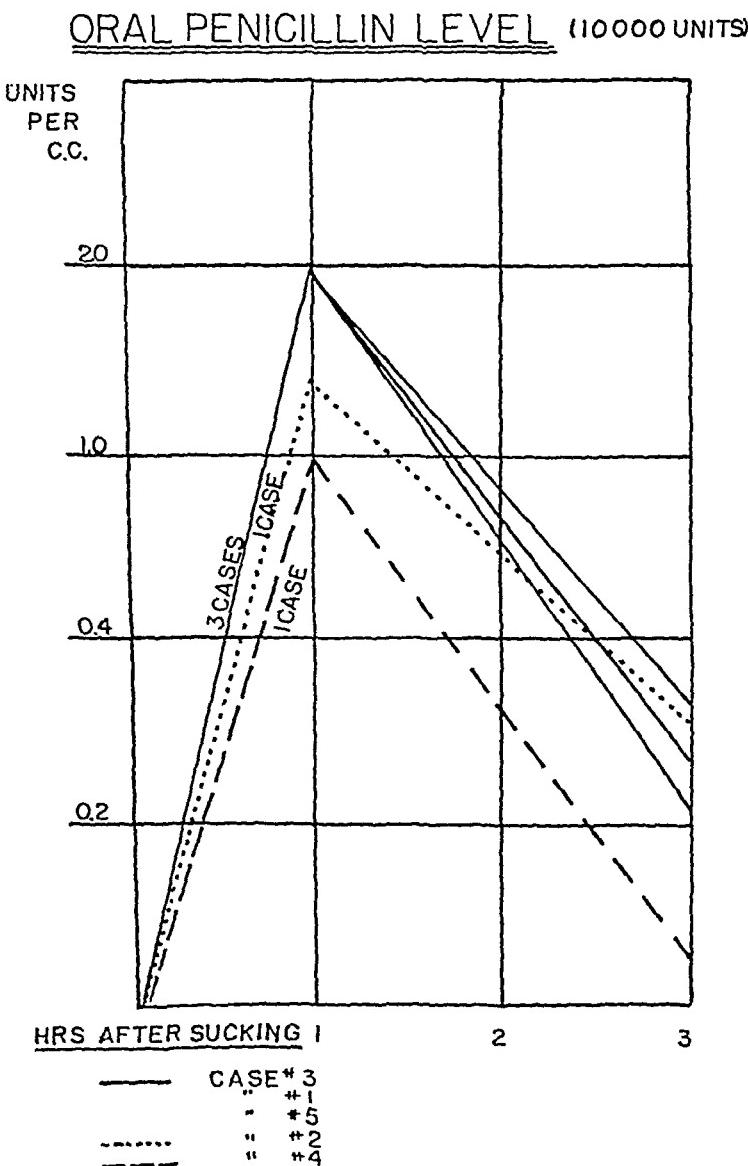


Fig. 2.

units were used. The results did not vary widely. While the 5,000 unit cases showed one who reached 2.0 units per cubic centimeter at the end of one hour, the 10,000 unit cases showed three who reached this level at the same interval. All the cases in both series exceeded 0.4 unit per cubic centimeter at the end of one hour. The level in all decreased substantially at the end of three hours. Some of the 5,000 unit cases neared zero and the one with the highest level dropped to 0.2 unit. The 10,000 unit cases showed an average level of 2.0 units per cubic centimeter at the end of one hour and at the end of the third hour an average of 0.2 to 0.3 unit of penicillin per cubic centimeter. As Rammelkamp and Keefer¹² have found that 0.3 unit of penicillin per cubic centimeter is the upper limit needed for bacteriostasis of susceptible bacteria, we found that there is a sufficient concentration of penicillin for oral bacteriostasis for almost three hours and that the 5,000 unit lozenge is adequate to maintain this.

Penicillin Level in the Blood.—Ten patients were studied to determine the penicillin level in the blood after the child had sucked penicillin lozenges. Five of these were given 5,000 units and five 10,000 units. In the 5,000 unit patients we found that in no case was there a sufficient concentration of penicillin in the blood to determine a level, even at the end of two hours. In the cases of those receiving 10,000 units, we found that two showed a blood penicillin level of 0.04 units per cubic centimeter at the end of the first hour. Two other cases showed the same level at the end of the second hour and one showed no penicillin level at the end of the first, second, or third hour.

We feel that 5,000 units is a sufficient dose, as it maintains an adequate throat level without establishing a blood level which might possibly desensitize the patient. Furthermore, the alternating high and low throat levels are desirable, as this results in preventing the growth of penicillin-fast organisms and also in allowing the growth of harmless saprophytes which might likewise have an inhibitory effect upon the growth of the harmful streptococci.

Nose and Throat Cultures.—Nose and throat cultures were taken during the eight months of study. At each monthly visit, the child received a general physical examination plus a routine nose and throat culture. If a growth of either *Streptococcus hemolyticus* or *Streptococcus viridans* appeared, the child was asked to appear for another culture within the week. If negative, the patient returned at the regular monthly visit. A sufficient supply of penicillin troches or placebo troches of similar size, taste, and shape to last one month was distributed to all the patients studied.

The results of this study showed four cases had a growth of *Str. hemolyticus*, thirty-four had one of *Str. viridans*, and four one of *Staph. aureus*, the rest showing nonpathogenic organisms. Three of the children receiving the penicillin troches had *Str. hemolyticus* in their throats at one visit only and only one of the controls had a like experience. Of those with *Str. viridans* culture, sixteen were receiving the penicillin and the other eighteen were controls. Of course, one must note that each child was instructed not to take a lozenge on the morning of the clinic session.

Two of the group harboring the *Str. hemolyticus* were Class III cardiae who were bedridden most of the time and at the visit before beginning the penicillin lozenges throat cultures were taken and one hour later a penicillin lozenge was administered, to be followed at the end of a two-hour interval by throat cultures. Interestingly, the first cultures revealed a growth of *Str. hemolyticus* and the next two cultures were free from this organism, showing beyond doubt the efficacy of the troche. In the one case, a white girl of 12 years had had an attack of acute rheumatic fever and carditis each year for the past four years. This year, under the penicillin troche treatment, she went for the first time without developing any active signs of rheumatic fever. In our opinion the penicillin troche was undoubtedly an important factor in the prevention of rheumatic fever in this case.

In only one case was a positive *Str. viridans* culture found at a second visit.

All of our patients tolerated the penicillin lozenges very well. There was no mouth soreness nor discomfort at any time and there was no objection to taking the pleasant tasting troche.

CONCLUSIONS

Penicillin troches of 5,000 units each, when held in the mouth, are sufficient to produce a penicillin level of from 0.5 to 2.0 units per cubic centimeter of throat secretion at the end of one hour and retained a sufficient level to produce bacterostasis of susceptible organisms for practically two hours.

The above process occurs without noticeably producing any penicillin level in the blood with the dosage described above.

By use of these penicillin troches the authors hope to prevent many of the *Str. hemolyticus* upper respiratory infections which are so frequently the precursors of recurrent attacks of rheumatic fever per se.

REFERENCES

1. Mustard, H. S.: Rheumatic Fever in the Perspective of Public Health, Am. J. Med. 2: 609-617, 1947.
2. Wilson, May G., and Lubschez, R.: Longevity in Rheumatic Fever. Based on the Experience of 1,042 Cases Observed Over a Period of Thirty Years, J. A. M. A. 138: 794-798, 1948.
3. Health Problems of School Age Children, Statis. Bull. Metrop. Life Insur. Co. 28: 4, 1947.
4. Maliner, M. M., and Amsterdam, S. D.: Oral Penicillin in the Prophylaxis of Recurrent Rheumatic Fever, J. PEDIAT. 31: 658-661, 1947.
5. Hansen, A. E.: Rheumatic Recrudescences: Diagnosis and Prevention, J. PEDIAT. 28: 296-308, 1946.
6. Holbrook, Col. W. P.: The Army Air Force's Rheumatic Fever Control Program, J. A. M. A. 126: 84-93, 1944.
7. Morgan, H.: U. S. Dep't. of Labor Proc. Oct. 5, 1943. Childrens' Bureau Pub. No. 308: 4, 1947.
8. Massell, B. F., Dow, J. W., and Jones, T. D.: Orally Administered Penicillin in Patients with Rheumatic Fever, J. A. M. A. 138: 1030-1036, 1948.
9. Ross, S., Burke, F. G., and Olansky, S.: Oral Administration of Penicillin: Its Use in 150 Cases, New England J. Med. 236: 817-820, 1947.
10. Baldwin, J. S.: Sulfadiazine Prophylaxis in Children and Adolescents with Inactive Rheumatic Fever, J. PEDIAT. 30: 284-288, 1947.
11. Levinson, S. A., and MacFate, R. P.: Clinical Laboratory Diagnosis, ed. 3, Philadelphia, 1946, Lea & Febiger.
12. Rammelkamp, C. H., and Keefer, C. S.: Penicillin: Its Antibacterial Effect in Whole Blood and Serum for the Hemolytic Streptococcus and Staphylococcus Aureus, J. Clin. Investigation 22: 649-657, 1943.

PANCREATIC ACHYLIA AND GLYCOSURIA DUE TO CYSTIC DISEASE OF THE PANCREAS IN A 9-YEAR-OLD CHILD

HERMAN ANFANGER, M.D., MURRAY H. BASS, M.D., ROBERT HEAVENRICH, M.D.,
AND JOHN J. BOOKMAN, M.D.*
NEW YORK, N. Y.

INTRODUCTION

CYSTIC disease of the pancreas at any age is an unusual finding. Except for cystic fibrosis of the pancreas in infants, there are not many cases reported. In a review of 6,708 autopsies at Guys Hospital in 1897, White¹ found only three cases of pancreatic cysts, and in 1921 Judd² reported forty-one cases of pancreatic cysts of all varieties from the records of the Mayo Clinic up to that date. The case to be presented and discussed is that of pancreatic achylia associated with glycosuria due to multiple cysts of the pancreas. We have been unable to find a description of a similar case in the medical literature.

CASE HISTORY

H. F. was a full-term, spontaneously delivered infant born June 13, 1938, weighing 5 pounds, 11 ounces. He was fed a formula of evaporated milk, Dextri-maltose, and water, and received supplementary vitamins from one week of age. There was no erythroblastosis or other apparent illness except hernias which were treated by truss. At 5 years he had measles and later the same year, mumps, without evidence of pancreatitis.

His father, aged 35 years, and brother, aged 5 years, are living and well. His mother, aged 35 years, has had five pregnancies. One newborn infant was an anencephalic monster, one was stillborn, and one died at 3 months of age of virus pneumonia. His mother has intermittently had glycosuria, and for three short periods had taken insulin. The first episode of glycosuria was twelve years ago; the second was after a miscarriage 11 months before the birth of our patient, and the third was during the second half of her pregnancy before the birth of the patient. She had no other illness during this pregnancy and the child showed no signs of hypoglycemia at birth. There is no history of other familial disease, including meconium ileus, cystic fibrosis of the pancreas, or polycystic kidneys.

The patient gained weight slowly and was always somewhat small in stature (Table I). Until his present illness, however, he was very sturdy and active. His appetite was always excellent. His caloric and vitamin intake was adequate. He had shown no intolerance to any foods. He had not had diarrhea, though his stools were frequently foul, nor had he been usually prone to respiratory disease.

In April, 1947, at the age of 9 years, the patient developed lower abdominal cramps and fever to 100.5° F. Six hours later he vomited. After being observed for twenty-four hours for possible appendicitis, he was admitted to a hospital with a diagnosis of intestinal obstruction. Laparotomy was performed. An irregular mass was found causing obstruction with impaction of feces from the splenic flexure to the duodenal-jejunal junction. Although this mass was thought by the surgeon to have no connection with the pancreas and to contain no large cysts, a biopsy was taken which was reported as "cystadenoma of the pancreas

From the Pediatrics Service of Dr. Murray H. Bass, The Mount Sinai Hospital, New York, N. Y.

*Well fellow in Medicine assigned to the Metabolic Division.

TABLE I

DATE	HEIGHT (INCHES)	WEIGHT (LB.)	AGE
June 13, 1938		5.7	Birth
Aug. 30, 1938	21½	8.0	7 weeks
Sept. 19, 1938	21½	8.6	10 weeks
Oct. 17, 1938	22½	10.2	14 weeks
Nov. 14, 1938	23½	10.9	18 weeks
Dec. 12, 1938	24½	11.7	22 weeks
Jan. 13, 1939	25½	12.6	26 weeks
Feb. 12, 1939	25½	13.3	30 weeks
Mar. 9, 1939	26½	13.4	34 weeks
June 3, 1945	43¾	35.5	7 yr.
July 9, 1945	44	38.7	7 yr. 1 mo.
Aug. 27, 1945	44½	38.7	7 yr. 2 mo.
Oct. 9, 1945	44½	41.2	7 yr. 8 mo.
Dec. 12, 1945	45	42.0	7 yr. 10 mo.
Aug. 20, 1946	47½	45.2	8 yr. 2 mo.
July 15, 1947		36.5	9 yr. 1 mo.
Aug. 15, 1947		36.7	9 yr. 2 mo.
Sept. 23, 1947		42.0	9 yr. 3 mo.
Oct. 15, 1947		42.2	9 yr. 4 mo.
Nov. 15, 1947		44.5	9 yr. 5 mo.
Dec. 15, 1947	47½	46.7	9 yr. 6 mo.
Jan. 15, 1948		52.5	9 yr. 7 mo.
Feb. 2, 1948		61	9 yr. 7½ mo.
Feb. 24, 1948		45	9 yr. 8 mo.
May 15, 1948	50	54	9 yr. 11 mo.
June 15, 1948		54	10 yr.
August 24, 1948		52	10 yr. 2 mo.

of unknown histologic nature and origin," without evidence of any inflammatory reaction. A normal appendix was removed and a cecostomy was also made at this operation.

The child made a good postoperative recovery and was discharged on the fifteenth postoperative day. The cecostomy was closing and the bowels were moving regularly, although no resection of the mass had been performed.

Ten days later the child again became acutely ill with nausea, vomiting, generalized abdominal cramps, and severe distention. He was afebrile. Diagnosis of intestinal obstruction was again made, and the cecostomy was reopened. Twelve hours later because of aggravation of abdominal pain and distention, he was reoperated upon. A volvulus with gangrene of 4 to 5 inches of ileum was found. The gangrenous segment was resected and the two ends of the gut were exteriorized. Further exploration was not done because of the patient's poor condition.

During his subsequent five weeks in the hospital, he lost 25 pounds despite "intensive treatment with whole blood, plasma, protein hydrolysates, and minerals."

Since a urinalysis had not been performed before the administration of intravenous glucose, it was not until all intravenous medication was stopped that it was discovered that his urine repeatedly contained sugar. In addition, it usually contained 1 to 2 plus albumin with few hyaline casts. The fasting blood sugar was 166 mg. per cent. Blood count, chest x-ray, and flat plate of the abdomen were normal. He received no insulin.

He returned home thirty-eight days after his operation and for the next three weeks ate very well but failed to improve. Although the cecostomy drained a small amount of watery fluid every few days, the ileostomy drained copious amounts of semifluid feces. The boy's psychologic adjustment to the ileostomy was good but he continued to be weak and severely emaciated and was, there-

fore, transferred to the Pediatric Service of The Mount Sinai Hospital, where he first came under our observation.

On admission on July 15, 1947, he was a pathetically emaciated, pale, chronically ill boy. There was marked wasting of subcutaneous tissue and musculature. He was too weak to sit up, yet he appeared unusually alert and intelligent. His axillary temperature was 99° F., and pulse 104, respiration 24, weight 36½ pounds (16.6 kilograms). There was generalized thinning of the hair, and the entire scalp, forehead, neck, and the eyelids were involved in a thick, dry, flaky, exfoliative dermatitis. Elsewhere the skin was similarly involved but to a lesser degree. The palpebral margins were thickened. His pupils reacted to light and accommodation. The fundi were normal. His lips were pale, but there was no cheilitis. His pharynx was bland and his tongue was not smooth. There was no general glandular enlargement. Examination of the chest revealed a few coarse râles over the left base posteriorly.

There was no impairment of resonance or fremitus, and no change in breath sounds. His brachial blood pressure was 90/60. The heart was not enlarged to percussion, the sounds were of good quality, and there were no murmurs. A sinus tachycardia was present. The abdomen was seaphoid and nontender. The liver, spleen, and kidneys could not be felt. There was a clean eecostomy in the right lower quadrant, draining a small amount of mucoid material. Just to the left and above the umbilicus there was a double-barreled ileostomy, from the proximal loops of which exuded semisolid feces. No abdominal mass could be felt. Rectal examination was negative. There was moderate clubbing of the fingers and toes. The deep tendon reflexes were hyperactive throughout, with unsustained ankle clonus. There was no disturbance of sensory perception.

Laboratory studies revealed: a white blood cell count of 15,400; segmented polymorphonuclears, 58 per cent, nonsegmented, 15 per cent; lymphocytes, 22 per cent; monocytes, 4 per cent; eosinophiles, 1 per cent.

The urine was yellow and acid, with a specific gravity of 1.024; it was albumin negative; there was one plus reducing substance identified as glucose; microscopically there were few uric acid crystals and no casts or cells; blood Wassermann was negative; Schick test was negative; Mantoux 1:10,000 was negative. X-rays of the chest, long bones and gall bladder showed no abnormalities.

Flat plate of the abdomen showed that: "Both kidneys are normal in size, shape and position. No urinary calculi noted or abdominal masses. No abnormality seen."

Intravenous pyelography showed no abnormalities.

Blood group was O, Rh positive.

Serum chloride was 91 meq. per liter; serum carbon-dioxide content, 27 meq. per liter; total serum protein, 6.3 Gm. per cent; hematocrit, 35 per cent; blood urea nitrogen, 10 mg. per cent; basal metabolic rate, plus 24 per cent Benedict-Roth (58 calories); culture of nasopharynx showed *Staphylococcus aureus* alpha and *Staphylococcus albus* beta; culture of ileostomy drainage showed *Bacillus coli*.

A barium enema revealed no obstruction of the colon up to the eecostomy. Examination of the lower bowel by passage of a Miller-Abbott tube inserted into the distal ileostomy demonstrated several loops of normal intestines. Thus patency of the lower bowel was proved and it was felt safe to let the colostomy close spontaneously.

A gastrointestinal series revealed a normal intestinal pattern down to the ileostomy, but when charcoal was given orally, it appeared in the ileostomy drainage in one and one-half hours. It was feared that this rapid transit time indicated a high ileostomy with a relatively small intestinal surface for absorption of food. Therefore a synthetic feeding was instilled into the distal ileostomy.

segment by continuous drip. This consisted of a high vitamin, high caloric mixture of carbohydrates, fats, partially hydrolyzed proteins, and electrolytes, and provided one calorie per cubic centimeter.

To demonstrate the absorption in the intestines proximal to the ileostomy, an oral glucose tolerance test was performed. The fasting blood sugar was 106 mg. per cent, with rise to 240 mg. per cent in one hour. Two subsequent glucose tolerance curves had fasting levels of 105 and 150 mg. per cent, respectively, increment rises of about 100 mg. per cent each after one hour, and gradual fall to fasting levels of the third hour (Table II). These studies demonstrated the child's mild glycosuria as well as his ability to absorb glucose.

TABLE II

DATE	DOSE GM. PER KG.	FASTING	1/2 HR.	1 HR.	2 HR.	3 HR.
7/18/47	1.75	160	200	240	145	100
10/29/47	2.5	105	185	200	125	100
11/11/47	2.5	150	---	260	250	50

To demonstrate the digestion and absorption of protein in the proximal segment of intestines, a gelatine tolerance test was performed, as described by West, Wilson, and Eyles.³ There was practically no increase in the blood amino acids in five hours. This indicated either that there was no trypsin in the intestines to digest the proteins to absorbable amino acids, that there was insufficient area of intestines to absorb the amino acids, or, finally, that the transit time of the food from the mouth to ileostomy opening was too fast to allow digestion and absorption.

As closure of the ileostomy was imperative, the immediate problem was to build the child up for operation. It was, therefore, planned to feed him by mouth, by constant drip by tube into the distal ileostomy, and, in addition, by vein. He was given a high calory diet with supplementary water-soluble vitamins, and he received blood, plasma, protein hydrolysates, electrolytes, and vitamins. He also was given liver extract intramuscularly. He was given as much as 4,300 calories daily. Despite this tremendous intake for a 36-pound child lying in bed, he failed to gain.

The role his glycosuria played in his emaciation was raised. For one week he was given 5 units of protamine zinc insulin, then 5 units of regular insulin twice a day for ten days, after which the dose was increased to 10 units twice a day, but the glycosuria continued to fluctuate markedly and unpredictably. There was no acetoneuria during this time. As there appeared to be no benefit from the insulin, it was discontinued.

The drainage from the ileostomy continued to be copious, and on one occasion, 800 c.c. of fluid were recovered in twenty-four hours by wringing out his ileostomy dressings. This must have represented a fraction of the total discharge, but represented 60 per cent of his oral intake, thus emphasizing the massive amount lost in this manner.

His stools were not weighed, but they too were large and contained an excess of starch and fat as shown microscopically. His failure to gain was, therefore, most likely due to impaired digestion aggravated by large ileostomy and cecostomy drainage.

Three weeks after admission, the boy developed an intercurrent pneumonia with temperature rise to 103° F. This was accompanied by a leucocytosis of 16,300. *Staphylococcus aureus* alpha and *Staphylococcus albus* beta were recovered from the nasopharynx. He was treated with aerosol and intramuscular penicillin. He improved but five days later developed jaundice. His urine showed bile and 1:40 urobilin. The icterus index was 16, blood bilirubin 1.0 mg. per

cent, Van den Bergh indirect positive, cephalin flocculation 3 plus, prothrombin index 48 per cent, cholesterol 130 mg. per cent, cholesterol esters 60 mg. per cent, and stool bile negative. No bile was demonstrated in the drainage from the ileostomy. It was thought this upset might have been due to an homologous serum hepatitis secondary to the blood and plasma he had received two and one-half to three months previously. He was placed on a low-fat diet and given 2.4 mg. vitamin K daily. Three weeks later after a mild course and loss of only 2 pounds, he recovered without clinical or laboratory evidence of liver disease.

During September, three months after admission and one month after hepatitis, the child's status remained unchanged. Because of his failure to improve, the child was operated on September 26 by Dr. John Garlock. At operation no mass could be felt. The pancreas appeared firmer than usual, normal in size, with tiny nodules throughout the whole organ. A biopsy was taken of the pancreas. The cecostomy was closed. The ileostomy was resected, an end-to-end anastomosis was accomplished, many bands and adhesions were lysed, and a Meckel's diverticulum was resected. All wounds were closed undrained.



Fig. 1.—Microscopic section of pancreatic biopsy taken from patient revealing numerous cysts lined by low, cuboidal epithelium and containing pink-staining, laminated material.

Biopsy of the pancreas consisted of a 1.5 by 1.5 cm. mass of white, glistening, translucent tissue made up of closely packed, cystlike nodules measuring 1 to 3 mm. each. Microscopically these cysts were lined by low cuboidal and flattened epithelium and contained pink-staining, laminated material. (Fig. 1.) The cysts were separated by connective tissue septa, showing occasional structure suggestive of Islands of Langerhans. There was no inflammatory reaction, no extensive perieystic fibrosis, no large cysts, and no calcium deposits. No typical acinar tissue was found in the biopsy specimen.

Postoperative recovery was complicated by severe right-sided pneumonia.

Despite the restitution of continuity of his intestinal tract, and even though he had a voracious appetite, the child failed to gain although his strength returned remarkably. A malfunctioning pancreas was thought a more likely cause for the failure to gain than was the small amount of intestines that had been removed, the low-grade chronic pulmonary infection, or the mild glycosuria. Studies of pancreatic function were, therefore, undertaken.

The blood amylase was normal, equivalent to 110 mg. of sugar. The stools microscopically showed fat and starch as well as undigested meat fibers. The dried stool fat was 48 per cent. The gelatin tolerance test was repeated. After the ingestion of gelatin there again was no rise in blood amino nitrogen. After the administration of glycine^a a single amino acid not requiring further trypic digestion, there was a prompt rise in blood amino acid nitrogen. This demonstrated a defect in protein digestion rather than impairment in absorption.

To demonstrate absorption of fat, a Vitamin A tolerance test was performed. After ingestion of 1 e.c. of oleum pereomorphum there was a low fasting level of 31 gamma per 100 ml. and no apparent absorption of the fat-soluble vitamin. The fasting blood carotene was also very low, 15 gamma per 100 ml. It is also of interest that when the child was given an equivalent amount of Vitamin A in a water-soluble form (Mead's Polyvitamin Dispersion), he still showed essentially no absorption.

Dr. David Dreiling assisted us in doing further pancreatic enzyme studies. Under fluoroscopic control, a double rubber tube was passed into the intestines so that aspiration could be made simultaneously from the stomach and duodenum. He found that even after the injection of secretin, the patient had no increased pancreatic secretion. Only traces of lipase and amylase were found, and there was no trypsin present.

TABLE III. BLOOD

DATE	VITAMIN A	CAROTENE	VITAMIN C	TOTAL PROTEIN	A/G
7/14/47	37	11	1.28	6.86	
10/21/47	Hrs. 31	15			3.33/3.53
	4	15			
	6	14			
	8	14			
10/31/47	16	18			
	25	16			
	17	12			
	12	10			
12/19/47			1.21		
1/15/48				7.39	
1/28/48	12	17			4.26/3.13
4/13/48	34	17	1.21		

METABOLISM STUDIES

The patient was transferred to the metabolism ward^b and there given a calculated high calorie, high protein diet without added vitamins. Urines and stools, the latter marked by charcoal, were collected daily and pooled for three-day periods. Urinary and fecal nitrogen were determined by the microkjeldahl method. Chemical analyses for urinary creatinine, amino acid nitrogen, thiamin, riboflavin and N^methylhistidineamide were done on the three-day pooled specimens. Urinary glucose determinations were made daily. Blood determinations for vitamin A, carotene, vitamin C, total protein, albumin and globulin fractions, glucose, and amino acid nitrogen were made as indicated.

Fig. 2 charts the results of the patient's weight, nitrogen and caloric intake, fecal and urinary nitrogen excretion, and nitrogen balance.

^aThis division under the direction of Dr. Herbert Pollack is supported in part by grants in aid from the American Dry Milk Institute, The American Butter and Egg Board, E. R. Squibb & Co., and the New York Foundation.

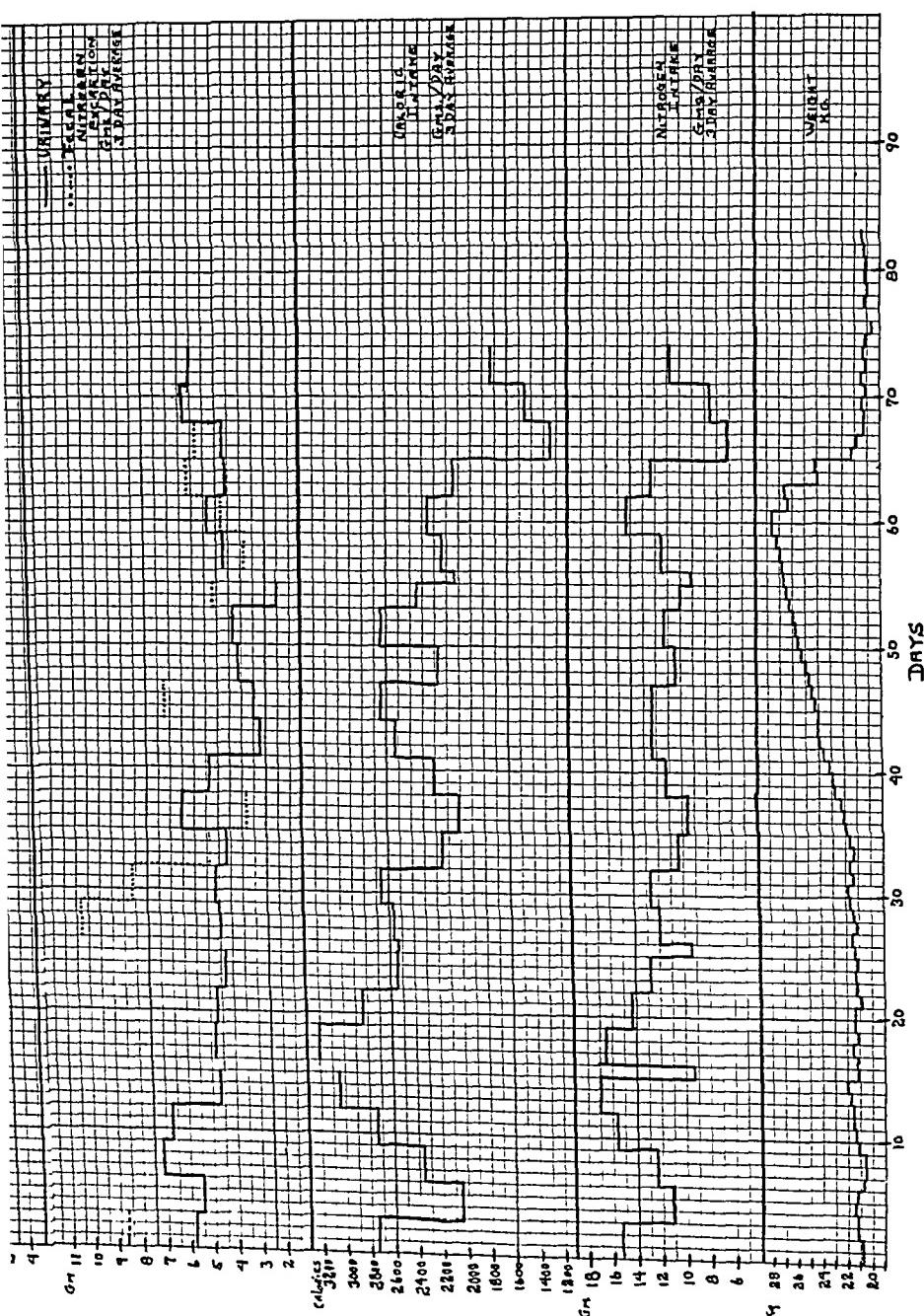


FIG. 2.—Nitrogen balance, urinary and fecal nitrogen excretion, caloric intake, protein intake, and body weight. On the thirty-sixth day of the study, while the patient was taking 2.8 Gm. protein per kilogram body weight, he began to gain weight. This continued until he contracted an upper respiratory infection on the sixty-first day, when precipitous drop in body weight occurred.

During the first five weeks of study, the child failed to gain weight. During this period he was receiving an average protein intake of 82.5 Gm. per day or 3.9 Gm. of protein per kilogram of body weight per day. Both the fecal bulk and fecal nitrogen decreased during this weight-gain period, but never to normal levels.

From the thirtieth day to the thirty-sixth day of observation, the patient received daily doses of 3 Gm. of enteric coated pancreatin. Within one day it was noted that whole or partly broken tablets were appearing in the stools. It had been noted that when charcoal was given by mouth it usually appeared in the stools in four to six hours and therefore it was felt that the rapid transit did not allow the alkaline intestinal secretions sufficient time to dissolve the enteric coating. Plain pancreatin powder in various mixtures was refused by the patient because of its unpalatability. Beginning on the fifty-seventh day, the patient received 3 Gm. of uncoated pancreatin tablets daily. During this period his weight continued to rise and his nitrogen balance was better than before. However, on the sixty-second day, he began to lose weight rapidly and two days later an evident upper respiratory infection with temperature rise to 101.8° F. appeared. Râles rapidly appeared in both lung fields and he was given intramuscular and aerosol penicillin. During this period of eight days he lost 7.3 kg.

While on the Metabolic Service he required no insulin. His glycosuria generally ranged from 0 to 5 Gm. per day with an occasional increase to 10 to 12 Gm. Acetonuria was never present.

Urinary vitamin excretion studies revealed that on the adequate intake of dietary nitrogen the patient excreted normal amounts of thiamin, riboflavin, and N'methylnicotinamide during his entire stay. The vitamin A and carotene levels remained essentially unchanged from those done while the patient was on the pediatric service where he was receiving supplementary vitamin A. His blood levels of vitamin C remained high throughout his hospitalization. It is apparent that the patient's ability to absorb the water-soluble vitamins was not impaired.

CLASSIFICATION OF PANCREATIC CYSTS

The classification of pancreatic cysts has been varied in the medical literature and it is beyond the scope of this paper to enter that phase of it completely. However, Walter and Clagett⁵ have organized a classification on an etiologic basis which is rather inclusive.

1. Cysts resulting from defective development :
 - (a) Cysts among infants
 - (b) Cysts associated with polycystic disease of the kidney
 - (c) Dermoid cysts
 - (d) Inclusion cysts
2. Cysts resulting from trauma (Pseudocysts)
3. Retention cysts
4. Neoplastic cysts
 - (a) Cystadenoma
 - (b) Cystadenocarcinoma
 - (c) Teratomatous cysts
5. Cysts resulting from parasites

A perusal of this classification placed our case possibly in one of three categories: (1) cysts among infants, (2) retention cysts, or (3) cysts associated with polycystic disease.

(1) CYSTS AMONG INFANTS

Under this category are included cases of congenital cystic fibrosis of the pancreas. Although this disease has many different clinical features, it is obvious that our case does not fit into this group. This boy had a normal infancy and childhood with fair weight gain and absence of fatty stools or pulmonary symptoms. Although there are several cases of cystic fibrosis of the pancreas described in older children, they practically all reveal nutritional or pulmonary difficulties in infancy and only rarely has there been described an associated glycosuria. Parmalee⁶ described a case of cystic fibrosis of the pancreas proved by autopsy in a 14-year-old child. She had had difficulty in feeding and steatorrhea in infancy but did well after 1½ years. At 11 years, however, symptoms recurred but there never was any associated glycosuria.

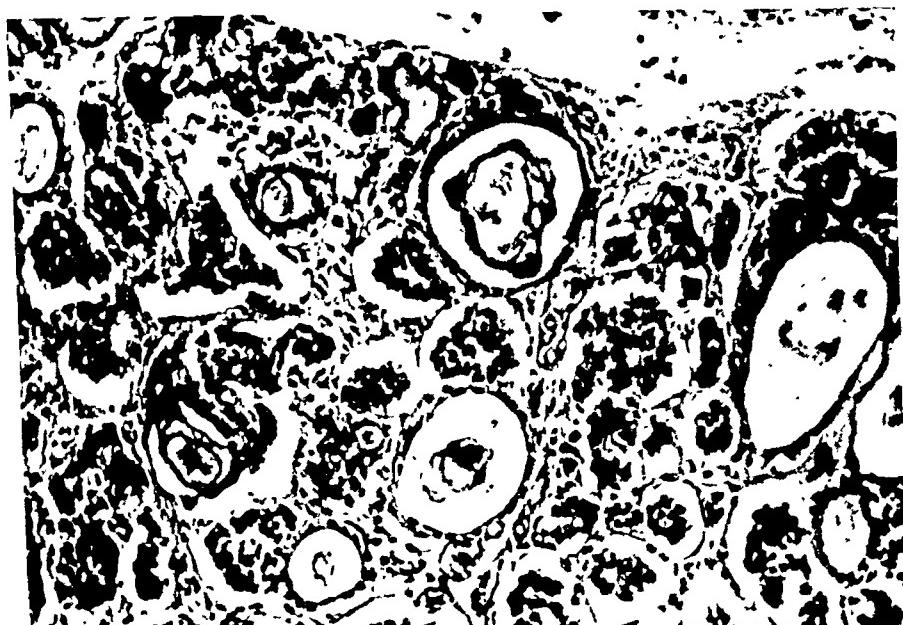


Fig. 3.—Microscopic section of cystic fibrosis of the pancreas revealing numerous small cysts with interspersed fibrotic changes. Islands of Langerhans are fairly numerous. This is to be compared with Fig. 1 for obvious dissimilarity.

Two biopsy specimens were taken from our patient at different times and neither one showed the characteristic changes seen in cystic fibrosis (Fig. 3). Microscopic examination of pancreatic tissue from cases of cystic fibrosis reveals much of the acinar tissue to be atrophic and replaced by proliferating fibrous and scar tissue, accompanied by varying amounts of acute and chronic inflammatory exudate. Islets of Langerhans are, as a rule, not significantly changed. In our patient (Fig. 1), there is no fibrous tissue interspersed between the numerous cysts. Although the two biopsies obtained account for only insignificant sections of the pancreas anatomically, still one can almost say with assurance that the rest of the pancreas must be similarly affected. Farber et al.⁷ reported two cases

of operative removal of approximately 70 to 80 per cent of the pancreas in children and in both these cases there was an adequate amount of pancreatic function present and diabetes did not occur. Lohbe, as quoted by Coope,⁸ reported a similar case operated upon and later confirmed by autopsy. Of the whole pancreas in an adult only a stump 2 cm. long and adherent to the duodenum remained after an earlier necrosis. Even this shred of tissue was affected by inflammatory reaction, yet extensive metabolic studies were done and no real evidence of impaired digestion found. Thus one can safely say that when pancreatic achylia occurs, almost the entire pancreas must be severely involved.



Fig. 4.—X-ray of chest revealing peripheral emphysema and hilar fibrosis.

(2) RETENTION CYSTS

Retention cysts have been described as resulting from an obstruction of larger or smaller ducts due to many causes. However, experimental evidence does not bear this out. Senn⁹ considers, as a result of his experiments on animals, that the closure of the pancreatic duct is not the only nor the most important cause of the development of pancreatic cysts. Among all the cases of lig-

tion of the pancreatic duct which he performed on different animals, he never saw the development of a pancreatic cyst or any tendency to such formation, although without doubt the portion of the pancreas which was cut off continued to secrete, as was shown by experiments in which external pancreatic fistulae were established. The single visible result of the closure was always a moderate dilatation of duct beyond the ligature. The most important etiologic factor in development of pancreatic cysts, says Senn, must be sought in hindrance to absorption of pancreatic juice by the admixture of pathologic nonabsorbing substances or a lessened activity of the absorbing vessels. Farber¹⁰ agrees with this view and feels it is the thick, gelatinous type of secretion seen in cystic fibrosis of the pancreas which primarily produces cystic changes. He proves this experimentally by repeated injections of pilocarpine in 6- to 8-week-old kittens, where pancreatic changes similar to those seen in cystic fibrosis of the pancreas were found to occur following these injections but not in control kittens.

(3) CYSTS ASSOCIATED WITH POLYCYSTIC DISEASE OF OTHER ORGANS

This is the rarest among cysts of the pancreas. Pathologists have used the term *dysontogenetic cysts* of the pancreas. This type of cyst occurs with other cysts of kidney, liver, and central nervous system. Lindau,¹¹ in his classic monograph, has described fifteen cases with polycystic disease of many organs. He found associated pancreatic cysts in eight of the fifteen cases and in two cases there was an associated glycosuria. In one microscopic section taken from a female adult the findings were similar to those in our case, but here there was no associated diabetes.

Although our patient reveals no clinical evidence of cerebral or renal cysts, yet the pathologic picture comes closest to that described by Lindau and probably falls in that group. There have never been any localizing cerebral symptoms in our patient and careful neurologic examination fails to reveal any evidence of cystic disease of the central nervous system. An intravenous pyelogram was also done and showed no abnormality of kidney or ureter.

The treatment of his glycosuria was never a complicated problem except for a short postoperative period when he developed acidosis which was easily treated with insulin and fluids intravenously. To date he is not taking insulin and intermittently spills 0 to 5 Gm. of sugar in his urine daily.

Whether this boy's glycosuria represented true diabetes is still open to question. It is true that he had three glucose tolerance tests which showed typically diabetic curves. However, his response to insulin was not typical. The other question that arises is whether he has had a subtotal destruction of his Islet cells due to pressure from cyst formation. This is only speculation and will not be gone into.

In cases of total excision of the pancreas¹² in adults there is usually a need of only 30 to 50 units of insulin daily. However, the amount of insulin necessary to control a child with complete excision of the pancreas has never been evaluated and conceivably is lower than this. It is also of interest that the patient's mother had mild diabetes while she was pregnant and this may have some bearing on the boy's pancreatic anomalies.

DIAGNOSIS OF PANCREATIC ACHYLLIA

Pancreatic achylia gives rise to many specific findings and abnormal metabolic changes. However, many of these so-called "specific findings" have not been consistently diagnostic and it seems worth while to outline them with a brief discussion of their significance. The usually quoted findings in pancreatic achylia are: (1) absence of pancreatic ferments; (2) steatorrhea and increased fat loss in the feces; (3) azotorrhea, increased nitrogen loss in the feces; (4) amylorrhea, increased carbohydrate loss in the feces; (5) flat gelatine tolerance test; (6) flat vitamin A tolerance test; (7) improvement of carbohydrate, fat, and protein metabolism with addition of oral pancreatic enzymes; (8) negative nitrogen balance.

1. *Pancreatic Ferments*.—The failure to demonstrate pancreatic enzymes upon duodenal aspiration does not of itself confirm the diagnosis of pancreatic achylia. This has been stressed by Bauman and Whipple,¹⁴ who believe that only after the injection of secretin or mecholyl should one come to any definite conclusions. Secretin induces a copious flow of pancreatic juice which is rather poor in ferments, and mecholyl, which produces a neural stimulation of the pancreas through the vagus nerves, gives rise to a more concentrated and richer ferment mixture. Our patient upon direct aspiration of duodenal juice had only traces of pancreatic ferments which showed no rise following secretin injection.

2. *Steatorrhea*.—The presence of steatorrhea alone is not diagnostic of pancreatic achylia. Steatorrhea occurs in many conditions, among them being simple diarrhea, celiac syndrome, sprue, biliary obstruction, and prematurity. Our patient had steatorrhea with dried stool containing 48 per cent total lipids.

3. *Azotorrhea*.—Neither the increased percentage of nitrogen in the stools nor the presence of meat fibers is diagnostic of pancreatic achylia. As shown by Pratt,¹⁵ the percentage of nitrogen in dried stools has proved to be of no definite value. There may be a relatively high content of nitrogen in the stool and yet the amount of dried stool may be so small that the absorption of nitrogen remains within normal limits. Beazell, Schmidt, and Ivy¹⁶ have also found large quantities of meat fibers in stools of patients with simple diarrhea where the total fecal nitrogen excretion was only slightly greater than normal. With few exceptions, however, as shown by Beazell, et al.,¹⁶ pancreatic achylia is characterized by noticeable simultaneous failure in absorption of fat and nitrogen. Our patient had an increased stool excretion of both fats and nitrogen.

4. *Amylorrhea*.—The presence of starch granules in the stool is also not diagnostic of pancreatic achylia. The starch intolerance type of celiac syndrome as described by Herter,¹⁷ Haas,¹⁸ and Andersen,¹⁹ frequently reveals the presence of starch granules. The failure of demonstration of starch granules should not make one hesitate to confirm the diagnosis of achylia pancreatica, since it is only infrequently found in these cases. Ptyalin, intestinal amylase, and colon bacteria are all instrumental in breaking down starch, and do it very well as a rule. In our patient fat droplets and meat fibers have been invariably found when he was on an unrestricted diet but starch granules on the contrary have only rarely been found in the stools during such periods.

5. *Gelatine Tolerance Test.*—This test, as has been shown by West, Wilson, and Eyles,³ is specific of trypsin deficiency. It depends upon the ingestion of gelatin and the determination of blood amino nitrogen levels. In the presence of trypsin deficiency there is no rise of blood amino nitrogen. The question of impaired intestinal amino acid absorption should be ruled out by means of a glycine tolerance test⁴ which uses glycine, a single amino acid, as the test substance, and then measures the rise in blood amino nitrogen. The absence of demonstrable tryptic activity by this test has only been found in cases of cystic fibrosis of the pancreas and pancreatic achylia. It was found in our patient.

6. *Vitamin A Tolerance Test.*—The finding of impaired vitamin A absorption can be used as a confirmatory test, but the poor assimilation of vitamin A is such a widespread finding as to make it nonspecific. There is a poor vitamin A absorption found in celiac syndrome, diarrhea, and even in certain allergic conditions. Two vitamin A tests using Oleum Percomorphum and Polyvitamin Dispersion showed impaired absorption in our patient.

7. *Addition of Pancreatic Enzymes.*—Although for the most part the addition of pancreatic enzymes orally has improved the digestion of protein, carbohydrates, and starches, and is considered by some authors as an essential feature, the literature is not entirely in agreement. Pratt, Lamson, and Marks,²⁰ Cruikshank,²¹ Nasset et al.,²² Selle,²³ Schmidt et al.²⁴ all observed a significant reduction in quality of nitrogen wasted in feces when adequate substitution therapy was tried. Coffey, Mann, and Bollman,²⁵ on the other hand, were unable to demonstrate any specific effect. In agreement with Seele,²³ the latter authors also found that enzyme therapy was without effect on the quantity of fat wasted in stool. Perhaps the reason for this disagreement may be the varying potencies of the specific enzymes in differently prepared preparations. Notorious is the low lipase content of most pancreatic preparations which accounts for the more frequent failure to improve the digestion of fat. Our patient did not show any striking improvement after the ingestion of pancreatic extract.

8. *Nitrogen Balance Studies.*—Studies of nitrogen balance are important in confirming the diagnosis of pancreatic achylia. Studies reported in the literature have been done on children with pancreatic achylia due to cystic fibrosis of the pancreas, and repeated observations have recorded the increased excretion of nitrogen in the stools of these patients.^{12, 26} As a result of our metabolic studies, it was felt that our patient could be kept in good nitrogen balance and could gain weight if a liberal, high calorie, high protein diet was given. He consumed large amounts of food until he developed an intercurrent respiratory infection, at which point he rapidly went into a negative nitrogen balance and lost weight precipitously. While in "good health," he was in positive balance when taking only 2.9 Gm. of protein per kilogram body weight, and yet, at another time, while taking 3.4 Gm. of protein per kilogram body weight, he was in negative balance. This rapid weight loss and reversal of nitrogen balance associated with infection in these patients has been previously noted.¹²

SUMMARY

The case of a 9-year-old, previously healthy boy is described; he developed intestinal obstruction and at operation presented an abdominal mass, which on

two separate biopsies proved to be pancreas studded with multiple small cysts. Microscopic examination revealed a different lesion from that seen in congenital cystic fibrosis of the pancreas, but closely resembling that found in polycystic disease as described by Lindau. Extreme emaciation and evidence of vitamin A deficiency were present. These were accompanied by pancreatic achylia, failure to absorb vitamin A, flat gelatine tolerance test, and the presence of glycosuria. Clinical, chemical, and metabolic studies of the case are reported. In a follow-up after one year, the patient's general condition is good although his height and weight are retarded and he is prone to develop upper respiratory infections with rapid loss of weight. His mild glycosuria persists. Cystic disease of the pancreas and tests for pancreatic function are discussed.

REFERENCES

1. White, W. H.: Diseases of the Pancreas, Guy's Hosp. Rep. 54: 17, 1897.
2. Judd, E. S.: Cysts of the Pancreas, Minnesota Med. 4: 75, 1921.
3. West, C. D., Wilson, J. L., and Lyles, R.: Blood Amino Nitrogen Levels Following Injection of Proteins and of a Protein Hydrolysate in Infants With Normal and With Deficient Pancreatic Function, Am. J. Dis. Child. 72: 251, 1946.
4. Ansfanger, H., and Heavenerich, R.: Amino Acid Tolerance Tests in Infants, Am. J. Dis. Child. 77: 425, 1949.
5. Walter, W., and Clagett, O. T.: Surgery of Pancreas, Cyclopedias of Medicine, Surgery, and Specialties, Vol. XI, Philadelphia, 1945, F. A. Davis Co., p. 25.
6. Parmalee, A. H.: Pathology of Steatorrhea, Am. J. Dis. Child. 50: 1418, 1935.
7. Farber, S., Schwachman, H. S., and Maddock, C. L.: Pancreatic Function and Diseases in Early Life, J. Clin. Investigation 22: 827, 1943.
8. Cope, R.: Diagnosis of Pancreatic Diseases, London, 1927, Oxford University Press.
9. Nothnagel's Encyclopedia of Practical Medicine, Vol. IX, Philadelphia, 1905, W. B. Saunders Co., p. 192.
10. Farber, S.: Experimental Production of Achylia Gastrica, Am. J. Dis. Child. 64: 953, 1942.
11. Lindau, A.: Studien über Kleinhirnerstenbau Pathogenese und Beziehungen zu angiomatosis Retinae, Acta. path. et microbiol. Scandinav. Suppl. I, p. 1, 1926.
12. May, C. D., and Lowe, C. U.: The Treatment of Fibrosis of the Pancreas in Infants and Children, Pediatrics 1: 159, 1948.
13. Dixon, C. F., Comfort, M. W., Lichman, A. L., and Benson, R. E.: Total Pancreatectomy for Carcinoma of the Pancreas in Diabetic, Arch. Surg. 52: 619, 1946.
14. Bauman, L., and Whipple, A. O.: Diagnostic Value of Pancreatic Function Tests, Am. J. M. Sc. 207: 281, 1944.
15. Pratt, J. A.: Study of Steatorrhea, Am. J. M. Sc. 187: 222, 1934.
16. Beazell, J. M., Schmidt, C. R., and Ivy, A. C.: The Diagnosis and Treatment of Achylia Pancreatica, J. A. M. A. 116: 2755, 1941.
17. Herter, C. A.: Infantilism From Chronic Intestinal Infection, New York, 1908, The Macmillan Co.
18. Haas, S. V.: The Value of the Banana in Treatment of Celiac Disease, Am. J. Dis. Child. 28: 421, 1921.
19. Andersen, D.: Celiac Syndrome, Starch Intolerance, J. PEDIAT. 30: 564, 1947.
20. Pratt, J. H., Lamson, P. D., and Marks, K. H.: The Effect of Excluding Pancreatic Juice From the Intestines, Tr. Am. Physician 24: 266, 1909.
21. Cruikshank, E. W. H.: Effect of Depancreatization on Digestion, Biochem. J. 9: 138, 1915.
22. Nasset, E. S., Pierce, H. B., and Murlin, J. R.: Influence of Yeast on Protein Metabolism in Normal and Depancreatized Dogs, J. Lab. & Clin. Med. 16: 115, 1931.
23. Selle, W. A.: The Effect of Enteric Coated Pancreatin on Fat and Protein Digestion of Depancreatized Dogs, J. Nutrition, 13: 15, 1937.
24. Schmidt, C. R., Beazell, J. M., Crittenden, P. J., and Ivy, A. C.: The Effect of Oral Administration of Pancreatin on Fecal Nitrogen and Fat Loss in Achylia Pancreatica, J. Nutrition 14: 513, 1937.
25. Coffey, R. J., Mann, F. C., and Bollman, J. L.: Substitution Therapy in Experimental Pancreatic Deficiency, Am. J. Digest. Dis. 7: 119, 1940.
26. Shohl, A. T., May, C., and Schwachman, H.: Studies of Nitrogen and Fat Metabolism in Infants With Pancreatic Fibrosis, J. PEDIAT. 23: 267, 1943.

GRID PRODROME PHENOMENON IN CELIAC DISEASE

REPORT OF FOUR CASES

ALLAN B. COLEMAN, M.D.
WASHINGTON, D. C.

THE pediatrician in his modern role of practitioner of preventive medicine is becoming increasingly interested in eliciting the earliest possible signs of pathologic processes. The popularity of the Wetzel Grid method¹ for the study of the nutrition and development of individuals, gained in a relatively few years, attests to this concept of pediatrics.

Wetzel¹ early pointed out the beginning signs of simple nutritive failure, as mirrored on the grid by "cross channelling" and "low angle drift." We wish to present a preliminary report of similar changes in relation to the incipient stages of true celiac disease, clearly demonstrable on the Wetzel grid months before the onset of recognizable clinical evidences of this well-known disease entity.

We have termed this early phase of the disease the *grid prodrome*. Although seen in the form of cross channelling, it is best demonstrated in the auxodrome panel of the grid, usually manifest as a more or less sharp departure of the curve from the previously established auxodrome of preferential growth rate. In some cases another sharp dip occurs, denoting celiac crisis, soon after the onset of clinically recognizable signs.

The patients to be reported were studied in retrospect as part of a series to be reported in detail elsewhere.² No prediction can be made, therefore, as to whether or not the appropriate diagnosis could have been established during the prodromal period and the course of the disease thereby altered.

REPORT OF CASES

CASE 1.—W. C., a white male infant, was delivered at term, weighing 6 pounds, 7 ounces. Weight loss and watery stools were first noted at the age of 6 months. He was admitted to Children's Hospital, aged 6½ months, where the important findings included foul, foamy stools containing excessive amounts of fat and starch. A gastrointestinal x-ray study showed the moulage sign.³ There was prompt clinical response to standard celiac dietary and vitamin therapy.

Fig. 1 illustrates this child's grid record. Here the grid onset antedated the clinical onset by two months, as indicated by the arrows.

CASE 2.—C. R., a white female infant, the result of a normal pregnancy, was born at term weighing 6 pounds, 7 ounces. Intermittent diarrhea began at approximately 7½ months of age. At the time of admission to Children's Hospital, aged 9 months, she showed typical celiac stools and characteristic body conformation; the duodenal enzymes were normal in amount. She responded to routine therapy for a time but was readmitted at 11 months of age in severe celiac crisis associated with a respiratory infection. Thereafter, improvement was steady.

From The Children's Hospital, and The Department of Pediatrics, George Washington University School of Medicine, Washington, D. C.

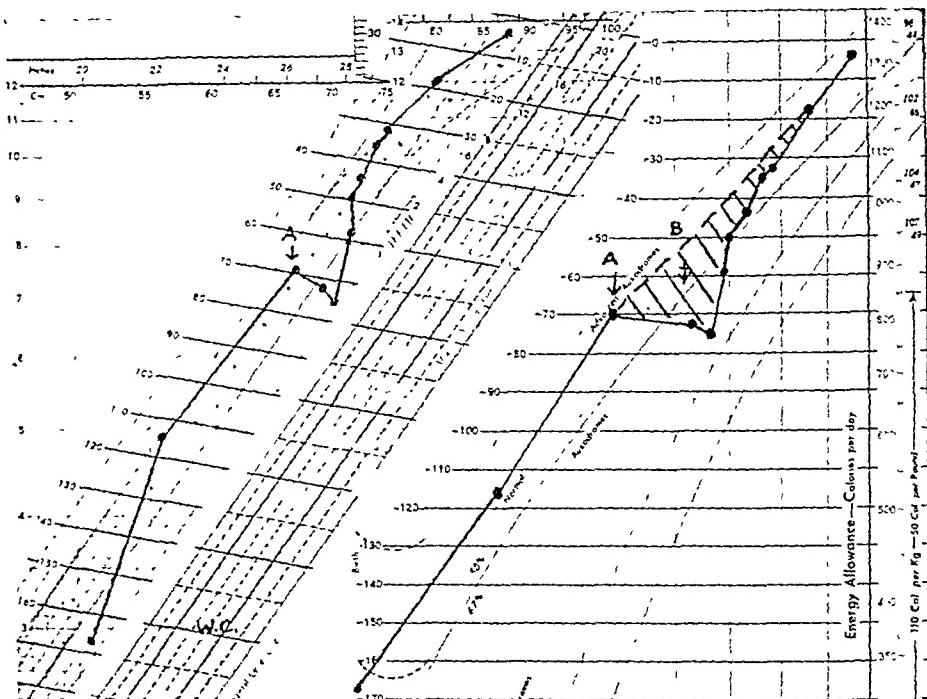


Fig. 1.—Wetzel grid record of W. C., showing grid onset (A) at age 1 months, as a sharp departure from physique channel and auxodrome. Clinical onset was at B, age $6\frac{1}{4}$ months. The interval A-B is the grid prodrome.

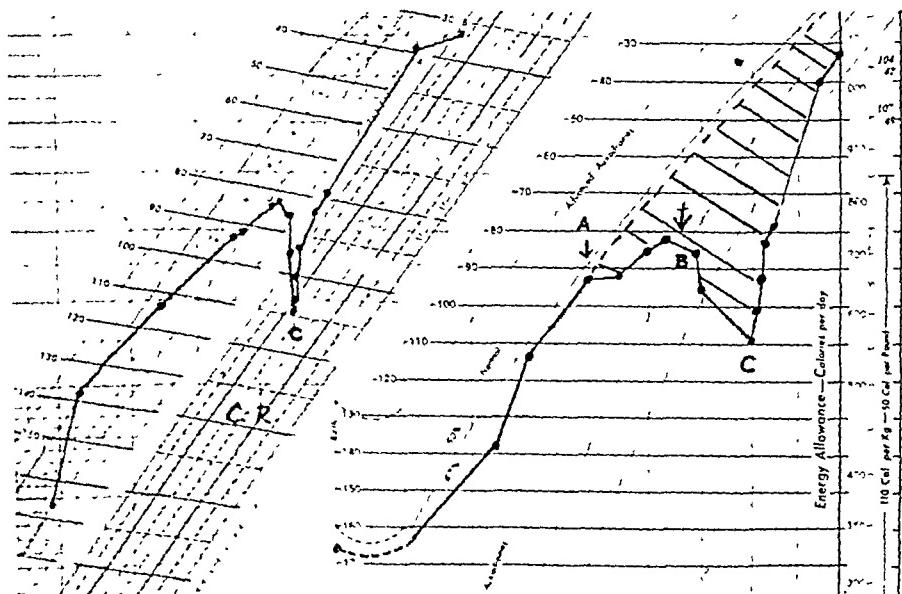


Fig. 2.—Record of C. R. on the Wetzel grid. The sharp departure from auxodrome at A is seen in the channel system only indistinctly. Clinical onset at B. Episode of celiac crisis at C is shown in the channel system as sudden weight loss. The interval A-B is the grid prodrome.

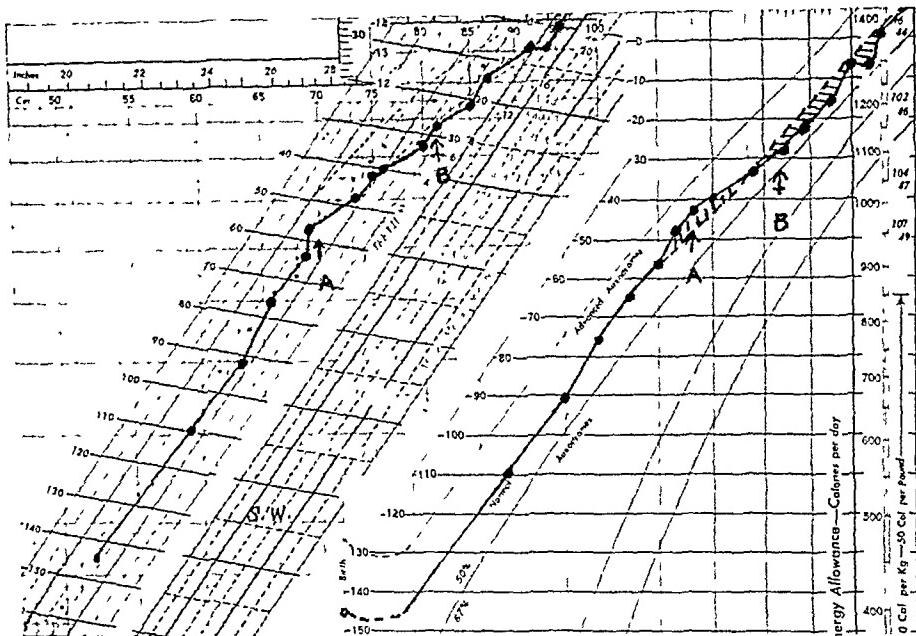


FIG. 3.—Record of S. W., a mild case of celiac disease. Grid onset at A, clinical onset at B; grid prodrome A-B. The brief episode of rapid weight gain preceding the grid onset has not been explained.

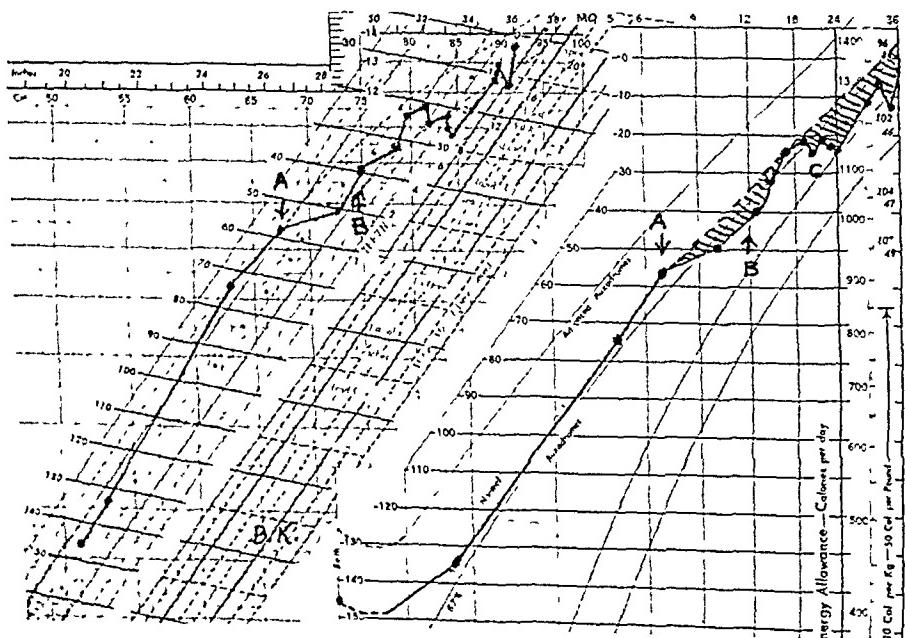


FIG. 4.—Grid record of B. K., showing grid onset at A, clinical onset at B, grid prodrome A-B, and first relapse C.

This patient's grid record is shown in Fig. 2. The arrows denote the grid onset which preceded the clinical onset by 3½ months. The episode of crisis at 11 months, associated with severe weight loss, is clearly seen.

CASE 3.—S. W., a white male infant, was born at term weighing 8 pounds, 1 ounce. He was believed to be well until 14 months of age, at which time intermittent diarrhea began. He quickly developed the potbellied habitus and characteristic stools. Except for minor setbacks, his response to routine therapy has been excellent.

Fig. 3 shows this patient's record, the arrows delineating the 5½-month prodrome. The initial period of weight gain, at the time of grid onset, and the relatively slight interference with linear growth as compared to weight gain, are unusual, and have not been explained on any basis other than the mild nature of the disease in this child, and probable imbalances in body fluid content.

CASE 4.—B. K., a white male infant, was born uneventfully at term, weighing 8 pounds. He had a brief episode of loose stools at 11 months of age, associated with a respiratory infection; by 1½ months of age he had typical large, fatty stools and celiac habitus. He improved slowly on celiac diet, with several setbacks.

Fig. 4 shows this child's grid record, the prodrome lasting about 4½ months. The initial relapse at 19 months of age is also seen.

SUMMARY AND CONCLUSIONS

Four cases of typical celiac disease and their growth curves on the Wetzel grid have been presented. They illustrate the grid prodrome phenomenon, in that the onset of nutritive failure was demonstrable on the grid from 2 to 5½ months before the onset of recognizable clinical symptoms of the disease.

The mechanism of the prodromal phase is unknown. We might guess that it represents a stage of very subtle change in growth, ordinarily overlooked, and associated with the earliest workings of the defect in absorption of foodstuffs which occurs in celiac disease. We do not consider the grid prodrome specific for, or pathognomonic of, any one disease entity, but feel that it probably will be observed in the incipient and usually overlooked stages of other diseases, especially those of a metabolic nature.

The prodrome was not observed in all cases of celiac disease studied.² The exact incidence of this phase must be determined subsequently in a larger series.

It should be emphasized that the chief value to the pediatrician of such methods as the Wetzel grid lies in just such early warning signs as we have illustrated, in order to prompt him toward extra vigilance in his management of these patients, and by so doing to recognize the significance of the ordinarily ignored earliest clinical evidences of abnormal processes.

The assistance of Drs. Joseph S. Wall and William A. Howard in the preparation of this paper is gratefully acknowledged.

REFERENCES

1. Wetzel, N. C.: J. A. M. A. 116: 1157, 1941.
2. Wetzel, N. C.: J. PEDIAT. 22: 82, 1943.
3. Wetzel, N. C.: J. PEDIAT. 22: 208, 1943.
4. Wetzel, N. C.: J. PEDIAT. 22: 329, 1943.
5. Wetzel, N. C.: J. PEDIAT. 29: 439, 1946.
6. Coleman, A. B.: Celiac Disease. A Developmental Study, Clin. Proc. Child. Hosp. To be published.
7. Kantor, J. L.: Arch. Int. Med. 65: 988, 1940.

STRICTURE OF THE URETHRA IN CHILDREN

MEREDITH F. CAMPBELL, M.D.

NEW YORK, N. Y.

A URETHRAL stricture is a pathologic diminution of the lumen or of the distensibility of this canal. If we include the external urethral meatus (the pinhole meatus), congenital strictures are of extremely high incidence both in male and female children. One-fifth (over 1,000 cases) of the children I have seen because of urologic disturbances suffered congenital urethral stricture either as the fundamental lesion or as an important coexisting one.* Obviously the condition merits serious consideration among the more important lesions of childhood and especially since its neglect may entail grave renal damage. Acquired strictures are largely the result of gonorrhreal infections and, though relatively rare, are of only slightly higher incidence than the traumatic variety.

CONGENITAL STRICTURE OF THE URETHRA

Pathology.—In the absence of infection, congenital urethral strictures are characterized simply by abnormal narrowing of the canal without localized periurethritis. These congenital narrowings are precisely similar to congenital strictures so often found in the ureters, biliary ducts, or gastrointestinal tract. Yet urinary infection commonly develops in these patients and with it periurethritis at the point of narrowing. This results in local leucocytic infiltration and ultimate laying down of a ring of scar.

The important as well as the vital pathologic consideration in urethral stricture is its effect upon the upper urinary tract and especially the kidneys, the ultimate destruction of which may be anticipated unless the obstruction is eradicated. Dilatation of the urethra proximal to the stricture ensues, and in some boys and girls with stricture of the meatus, we have found the entire urethra enormously dilated (Fig. 1). In some instances only the posterior urethra is greatly distended. In a 5-month-old boy, a large diverticulum of the anterior bulbous urethra nearly disappeared following wide meatotomy and dilation of the congenitally stenosed meatus. A diverticulum of the same cause was observed in a newborn male in the region of the frenum. As the obstruction persists and increases, the bladder becomes dilated and trabeculated (Figs. 2 and 4); increasing urinary back pressure causes the uretero-vesical valve mechanism to give way. The ureters become progressively

From the Department of Urology, New York University College of Medicine.

*A canvass of several urologists performing a large number of transurethral prostatic resections discloses that 8 to 10 per cent of these patients have a small meatus, presumably congenital and requiring meatotomy. In a smaller number there is urethral stricture in the absence of a history of urethritis or urethral trauma and, therefore, presumably congenital. In many other males a small meatus passes unrecognized until the acquisition of gonorrhea. Moreover, stricture of the urethra in adult females is an extremely common finding, the clinical manifestations of which usually cause the diagnosis of "cystitis" to be made, and often the history of the condition dates to childhood. In short, the fact that these congenital strictures cause no prominent symptoms in infancy or childhood may have been a detriment to the patient, permitting unrecognized, obstructive, uropathic changes to progress.

dilated laterally and, by longitudinal dilatation, elongated and secondarily kinked (Fig. 3). Hydrourephrosis develops and, in advanced cases, the kidneys may be reduced to thin, scarred shells with little excretion. Unrelieved, the patient may be expected ultimately to die in uremia or urinary sepsis. In several cases of stricture of the external meatus, we have cystographically demonstrated wide dilation of the entire upper urinary tract.



Fig. 1.—Cystogram in congenital stenosis of the external meatus in a 7-year old boy. Bladder trabeculation is indicated by irregularity of contour. Urethral dilation is extreme, especially in the posterior portion. Micturition cured.



Fig. 2.—1. Marked thickening of the bladder wall in a 3-year old boy with congenital stenosis of external urethral meatus. Micturition *P*. Cystogram two years after *A*. During this interval, the urethra of the stenosed meatus had been kept widely dilated. There is still cystographic evidence of the obstructive uropathy but the condition of the bladder wall shows marked improvement.



Fig. 3.—Congenital stenosis of external urethral meatus in an 18-month-old male infant with balanitic hypospadias. The bladder was chronically overdistended with 500 c.c. urine. Excretory urogram shows marked dilation of upper urinary tract, particularly left hydronephrosis and vesical overdistention. Meatotomy. Indwelling catheter was employed for two weeks.



Fig. 4.—Vesical dilation, hypertrophy, trabeculation, and sacculation in a 13-month-old girl with congenital stricture of the anterior urethra.

(Fig. 3) which disappeared following simple meatotomy and the passage of sounds.

Symptoms.—The symptoms of congenital urethral stricture are predominantly those of obstruction with urinary difficulty, frequency, hesitancy, often terminal dribbling, and occasionally hematuria. The condition usually produces no symptoms until the second or third year of life, but may be manifest during early infancy. There is straining to void, the stream is extremely small, and with stenosis of the external meatus it may be threadlike and projected a great distance. Urination is sometimes intermittent and is generally painful. A recurrent, mucoid discharge may be noted. Hernia may result from excessive straining. A great many of the children the writer has seen with congenital urethral stricture were referred because of so-called enuresis, though with eradication of the stricture the dysfunction has usually disappeared.

With progressive renal injury by urinary backpressure with or without complicating infection, the systemic manifestations of urinary toxemia appear chiefly as gastrointestinal disturbances, anorexia, or failure to grow. Hyperirritability or sluggishness may result from toxic effects on the central nervous system. With the advent of infection there may be fever; the diagnosis "pyelitis" is usually then made.

Ulcerative meatitis is a frequent complication of congenital stricture of the urethral meatus in young boys.¹ There is superficial ulceration, a scab forms, this is wiped off by the clothing, and bleeding ensues. Parenthetically, it is this bleeding which, more than any other manifestation, is likely to direct attention to the condition. Healing occurs, the lumen is still further narrowed by the resulting scarring, and the cycle repeats itself. This condition has received considerable attention in pediatric literature, it having been believed by some that ulcerative meatitis results from dietary factors such as too much cream, while many have attributed it to the ammoniacal diaper with irritating urinary decomposition. Yet I have seen the condition in many boys long out of diapers and firmly believe congenital stenosis of the meatus is the basic lesion. The therapeutic test seems confirmatory for I have never seen a case of ulcerative meatitis which could not be cured promptly by wide meatotomy and maintenance of a wide open meatus. Although congenital stenosis of the external meatus is said to occur only in circumcised boys, I have seen it in the uncircumcised, but in the latter group there is no scab formation because the ulcer does not have the opportunity to dry. Most of the girls I have seen with congenital stricture of the urethra were referred for examination because of either persistent pyuria or so-called enuresis.

Diagnosis.—The diagnosis of stricture of the external urethral meatus in boys is readily made by observation of the pinhole-sized orifice. Yet in some of these cases the tightest portion of the meatal stricture is 2 or 3 mm. inside the orifice, and here the lesion is recognized at once by the passage of small sounds. Congenital strictures deeper in the urethra are diagnosed by difficulty of passage of small sounds, catheters, or bougies, and when the canal has been

adequately dilated to permit the introduction of a miniature urethroscope, the lesion may be visualized. In stricture, the instrument is grasped by the lesion. When the congenital stricture is located in the body of the urethral canal, it is often in the anterior bulbous urethra and may extend a centimeter or more. The bulbomembranous urethra is next in incidence as the site of congenital urethral stricture; congenital contracture of the bladder neck is fundamentally the same lesion—simply a congenital narrowing of the vesical orifice. In the extremely rare cases of congenital localized total occlusion of the urethra, there is an exaggeration of the same embryologic malformation in closure of the urethral gutter which produces congenital stricture.

The diagnosis of congenital urethral stricture in the female patient is suggested by difficulty of passage of small sounds which are grasped by the stricture. Yet the site and character of these strictures can readily be demonstrated by urethroscopy. If an irrigating type of urethroscope is used and this is recommended, there should be a small inflow of water at the time of the examination. Usually the strictured area will show rigid urethral walls and loss of striae and appear as a blanched, constricting ring, the surface of which may show congestion, desquamation, erosion, ulceration, or low superficial granulation. It may also show the trauma of preliminary instrumental dilation with bleeding. In the diagnosis of urethral stricture we prefer to employ small sounds rather than small bulbous urethral bougies, and try to confirm the diagnosis as often as possible by urethroscopy.

Treatment.—Congenital stenosis of the external meatus in boys is best treated by liberal meatotomy. This is readily performed in the office without anesthesia and if done quickly while the glans is firmly compressed between the thumb and first finger, is essentially painless (Fig. 5). Often the stenosed meatal opening is too small to permit the introduction of the tip of the knife blade, so that preliminary dilation with a probe or 4 F. or 5 F. sound is necessary. A No. 11 or No. 15 Bard-Parker knife blade serves admirably; the tip of the knife must be small enough to be introduced into the urethra at least 5 or 6 mm. Having widely incised the meatus downward, one can pass suitable-sized sounds to insure that the cut is adequate; the incised meatus of a 6-month-old boy should accommodate at least a 14 F. sound at the tip, and a 4-year-old boy should accommodate at least an 18 F. sound. Sounds of 10 F. and 14 F. should be passed to the bladder in these respective age groups to be certain there is no other congenital obstruction. Sharp-pointed scissors may be used for making the cut but the knife is my preference. Sutures are unnecessary. Brief, copious bleeding follows the incision but usually ceases shortly. Should it persist, this bleeding is readily controlled by compression of the glans for two or three minutes. No dressing is required following meatotomy although we customarily fasten a small piece of cotton over the end of the penis for thirty minutes until all bleeding has ceased. The object of this is to keep the child's clothing clean. The mother or nurse should be instructed to separate the incised surfaces of the meatus daily. After a week, the meatus should be widely dilated with sounds, and again in ten to

fourteen days, and at such times thereafter as may seem necessary to maintain a widely patent channel. The greatest difficulty encountered in the treatment of meatal stenosis is rapid healing together of the incised surfaces so that not infrequently a second meatotomy is necessary for a week or two. As in the treatment of all varieties of strictures, the condition is cured only when the strictured area remains widely and permanently dilated.

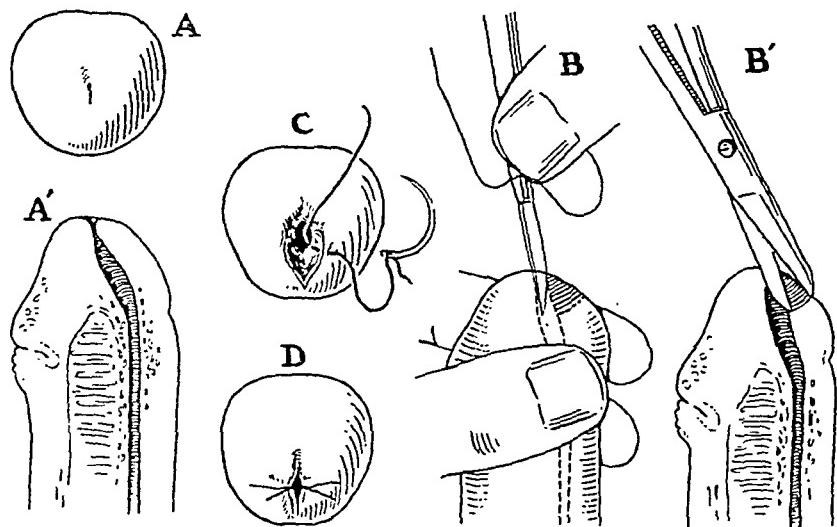


Fig. 5.—Meatotomy. *A, A'*, Minute meatus. *B*, Meatotomy with scalpel. If the glans is squeezed tightly simultaneous with the cut, the latter is almost always painless. *B'*, Meatotomy with scissors, but the knife is preferred. *C* and *D*, Suture of urethral mucosa to skin to prevent closure of the orifice healing, but this is unnecessary in children.

Congenital strictures located elsewhere in the urethra are best treated by dilation with sounds. Sometimes this means that the initial dilation must begin with an instrument as small as 4 or 5 F., gradually increasing the dilation as the caliber of the stricture permits, and without trauma. The urethra of the 6-month-old male infant should be dilatable at least to 10 F., and that of the 4-year-old male child at least to 14 F. The young female urethra will readily take sizes 2 F. to 3 F. larger. Stricture of the external meatus in the female practically never requires meatotomy and will almost always respond readily to periodic, progressive dilation with sounds.

Since the commonly employed curved or straight steel sounds regularly employed in adult patients are needlessly large and do not correspond in their curvature to the anatomic deep urethral curve of young male patients, the author devised a set of miniature sounds with short, sharply curved beak which represents a modification of the Van Buren sound adapted to the anatomic requisites of the young male urethra (Fig. 6^o).² Because the urethra in the young girl is so short, I employ these miniature sounds in these patients as well.

*Manufactured by J. Sklar Manufacturing Company, Long Island City, N. Y.

Urethrotomy, either internal or external, should practically never be necessary for the treatment of congenital stricture in the young except in those rare instances of total or near-total occlusion of the urethra or, in short, when no instrument can be passed through the urethra to the bladder or dilation is unsuccessful. Yet occasionally the infant can be spared operation by gentle, forceful manipulation and good fortune on the part of the instrumenteur. In two newborn male infants aged 8 and 24 hours with complete occlusion of the deep bulbous urethra and distended bladder, a 6 F. sound was forced through the solid obstructing mucosal curtain, after which the urethra was further dilated to 8 F. and an indwelling catheter inserted for forty-eight hours. Subsequent periodic dilation was curative. If this maneuver is unsuccessful, urinary extravasation is almost certain to ensue and require prompt perineal urethrotomy, at which time the patency of the entire urethra can be established.



Fig. 6.—Campbell miniature sound compared with adult Van Buren instrument.

When the stricture cannot be penetrated, an exploratory sound is passed as far as possible into the urethra and the urethrotomy incision is made against the tip of the instrument, even though this may mean opening the pendulous portion. Following wide incision of the stricture, a catheter is left indwelling in the urethra for three days to keep the incised edges of the stricture ring separated. Beginning about the fifth or sixth day postoperatively, periodic, progressive dilation with sounds is employed to achieve and maintain adequate urethral caliber.

When the lumen of the congenitally occluded urethra cannot thus be established, prompt perineal urethrotomy or cystostomy should be performed at once to obtain free bladder drainage, and at a later date the urethroplasty necessary to construct a patent canal is carried out.

ACQUIRED URETHRAL STRICTURE

Gonorrhreal urethritis accounts for most acquired strictures of the urethra in infants and children, but the nature of the lesion is often overlooked. A physician's 8-year-old boy was brought for examination because of enuresis. Despite his previous examination by several pediatricians and two urologists, a filiform caliber gonorrhreal stricture of the anterior bulbous urethra had been overlooked (Fig. 7). With conservative, progressive dilation his symptoms promptly disappeared and ultimately the stricture was cured. The gonorrhea occurred at 2 years of age and presumably was a nurse-girl infection. The

pathogenesis of gonorrhreal urethral stricture in the young is the same as in older patients. The columnar epithelium of the anterior urethra favors the growth and propagation of the gonococcus but stricture rarely occurs unless there is an intense, localized lesion with periurethritis, or treatment has been unduly traumatic. In the soft infiltration stage of periurethritis and stricture formation there is productive inflammatory reaction with subsequent organization of the exudate and the deposition of a variable amount of scar. There is slight sclerosis of the urethral walls as indicated by diminution of the normal folds and striae. This is the ideal time to achieve cure of the stricture by dilation with sounds. As the inflammatory process continues, there is further deposition of connective tissue so that the resulting scar must often be incised to achieve the desired urethral caliber. Urethral strictures, whether due to gonorrhea or nongonorrhreal infections or associated with vaginitis, are often multiple and are almost always anterior to the membranous urethra. This scar manifests its inherent tendency to contract and insidiously causes grave urinary obstruction. Usually inflammatory stricture develops slowly, but in a boy with gonorrhea at 11 months of age a filiform caliber stricture at the peno-sciatal junction was present at 22 months of age.



Fig. 7.—Postgonorrhreal stricture in an 8-year-old boy examined because of enuresis; gonorrhea at 2 years

The symptoms of acquired stricture appear insidiously with slightly increased frequency of urination later to be followed by urinary difficulty and terminal dribbling. The clinical manifestations and diagnosis are the same as described under congenital strictures. Treatment likewise is identical but gonor-

rheal stricture more often has to be cut, and if complicated by abscess, drainage is required. Stricture of the pendulous urethra not responding to dilation and not accompanied by periurethral abscess should be cut on the roof by internal urethrotomy. Deep bulbous or bulbomembranous strictures requiring urethrotomy are attacked by the perineal route. Yet even after surgical urethrotomy, the caliber of the urethra must be maintained by periodic progressive dilation until such time as the stricture remains fully dilated, for only then can it be considered cured.

TRAUMATIC STRICTURE

Most of these are the result of perineal straddle injuries or occur as complications of pelvic fracture. In children, the incidence usually follows the curve of traffic injuries. Straddle injuries most often involve the membranous urethra and there is frequently urinary extravasation immediately following the trauma. With healing of the traumatic lesion there is a residuum of dense periurethral infiltrate, and subsequent sclerosis forms the stricture. A young boy I saw had been hit in the penis with a basketball, causing rupture of the anterior bulbous segment with wide extravasation; stricture followed but was readily controlled by dilation. Since traumatic stricture always follows severe injury of the urethra, such injured patients should be observed and prophylactically dilated periodically for a number of years to be certain there is no interference with urethral drainage. Occasionally in localized traumatic stricture of the deep bulbous urethra excision of the scar-bearing area with end-to-end anastomosis of the urethra is successful.

Instrumental traumatic stricture of the urethra has been more commonly observed by me than any other form of trauma. This is due to failure of the instrumenteur to exhibit proper delicacy and gentleness in the passage of instruments as well as an absolute respect for the urethral caliber in selection of the size instrument he will employ. Several children have been seen with severe traumatic strictures of the bulbous urethra following cystoscopic instrumentation months or years before and, in at least two instances, I was responsible. Yet probably the greatest horror of this variety to come to my attention was a young boy whose urethra was densely strictured from end to end following cystoscopy months before in one of our leading medical institutions. Here a cystoscope entirely too large for this young boy's urethra had been employed, with a consequent ripping of the mucosa from meatus to bladder outlet. Parenthetically, trauma can be avoided in such a case by performing the cystoscopy through a perineal external urethrotomy opening. We have observed stricture to occur in some instances particularly at the meatus, following the protracted use of the indwelling urethral catheter.

Ocasionally the urethra is injured by the self-introduction of traumatizing objects into the channel—pins, needles, sticks, glass rods, and so forth, in both sexes. In one instance, the mother tied a string about the base of the penis of a 5-year-old boy with acute gonorrhea, to stop the discharge. This resulted in penile thrombosis, periurethral abscess, urethral fistula, and filiform

stricture. The condition was corrected by removal of the constriction, wide incision of the thrombosed structures, and periodic, progressive dilation of the stricture with sounds.

Prognosis.—The prognosis of all types of stricture is dependent upon the pertinacity with which periodic dilation of the urethra is performed. With proper follow-through in these cases, cure of the stricture usually can be anticipated, but most patients with even moderately severe stricture should have the benefit of annual or even semiannual dilation for many years. Failing in this, operation, reoperation, extravasation, or fatal urinary sepsis may be expected.

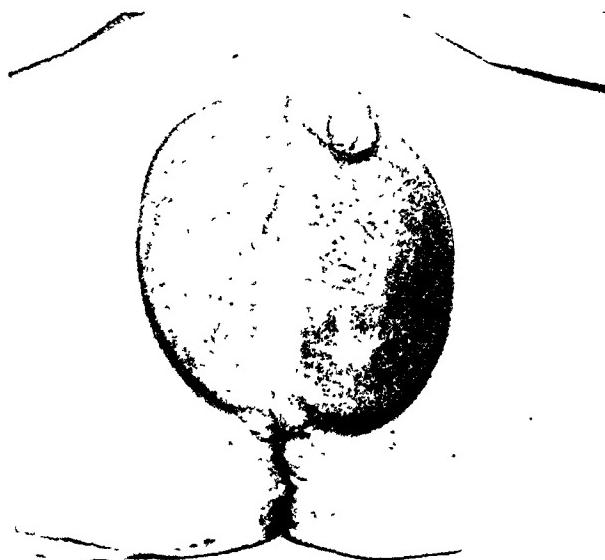


Fig. 8.—Extravasation occurring at site of surgical stricture following perineal closure of urethrorectal fistula in a boy of 7 years.

COMPLICATION OF STRICTURE

Ulcerative meatitis has been discussed. Acute periurethritis, even progressing to periurethral abscesses, may occur at the site of stricture upon acquisition of fresh infection or exacerbation of a smoldering one, and particularly when there is increased urethral constriction or external trauma. Yet with the liberal employment of present-day chemotherapy and antibiotic therapy, such complications should occur rarely or not at all. If the condition remains a periurethritis, its resolution can be greatly accelerated by periodic urethral dilation. If the lesion progresses to abscess formation, external drainage and urethrotomy are necessary.

Fistula will rarely follow external urethrotomy if periodic dilation of the canal is maintained postoperatively. Even in the young, prostatitis regularly

accompanies urethral stricture, and epididymitis, acute prostatitis, or urinary extravasation occasionally occurs. Urinary extravasation is most likely to occur in the children with traumatic stricture (Fig. 8).

SUMMARY

If we include the congenital variety, notably of the external urethral meatus, urethral stricture is of high incidence in children of both sexes. Back-pressure damage of the kidneys, and particularly when there is complicating renal infection, is the vital clinical consideration in urethral stricture. As the narrowing and blockage increase the renal damage is accelerated. Symptoms of stricture are essentially the same in the congenital or acquired varieties and are fundamentally due to obstruction. Congenital stricture of the external meatus is readily recognized by inspection alone, and by gentle, intelligent instrumentation all varieties of stricture elsewhere in the urethra can be readily identified. The most satisfactory treatment is periodic, progressive dilation with steel sounds; urethrotomy seldom should be required in urethral stricture in children and almost exclusively for the treatment of the traumatic variety.

REFERENCES

1. Campbell, M. F.: J. Urol. 50: 740-746, 1943.
2. Campbell, M. F.: J. Urol. 60: 653, 1948.

CONGENITAL ANAL STRICTURE

JOSEPH LIBURT, M.D.*
HUNTINGTON, N. Y.

CONTRARY to popular conception, congenital anal stricture or stenosis with its sequel of anal fissure or ulcer is comparatively common. Frequently missed for lack of systematic examination of the rectum in the newborn infant, these malformations may go unobserved. Daniels states that "unless they produce mechanical impediment to alimentation or become incompatible to life, they may not come to the attention of the attending physician; hence no accurate statistics are available."

In general, statistics on malformations of the anus and rectum point to an incidence of 1 in 10,000 births: but investigation will always show these figures refer to imperforate anus and rectum, or to congenital abnormalities existing between the anorectum and urogenital organs. As examples of statistical variations with reference to congenital anal stricture, Webb noted four cases in 150 consecutive deliveries, and Zahorsky found a palpable ring in fifteen out of sixty cases brought to his attention for anorectal complaints. Of sixty-one cases of anorectal conditions in infants and young children seen in my own practice during the past three years, the breakdown revealed:

Imperforate anus	1
Anal fissure	14
Anal ulcer	8
Anal cryptitis	12
Anorectal polyps	2
Prolapse of rectum	2
Congenital anal stricture	22

Accurate statistics on varying degrees of congenital anal stricture could be available only if a digital examination were performed on every newborn infant following delivery. The importance of such examinations cannot be overestimated; for it is only in the early stages that we may hope to remedy the cases of complete occlusion, and it is at this stage also that much can be done to prevent the minor malformations from proving serious in later life.

Tuttle states that the anus may appear perfectly normal on superficial observation, but examination will show it to be unusually narrow at some portion. This narrowing may take place at any point from the anal orifice to its junction with the rectum, or it may extend throughout the whole length of the anus. Since the length of the anal canal varies from 1 to 3.1 cm. with the lower limit prevailing in infants and young children, the impediment is found as soon as the finger is inserted into the canal. It may be at or just inside the aperture. In my own cases, the strictures were located anywhere from 1 to 3 cm. proximal

*Chief of Proctology, Huntington Hospital.

to the anal orifice, with an average depth of 1.5 cm. The narrowing may be annular and very short, being formed by bands or membranes extending from one side of the anus to the other, or it may appear to have a sickle or diaphragmatic-like appearance. This condition differs from the narrowing of later life produced by pathologic causes in that there is no hypertrophy of connective tissue, no cicatricial tissue, and no hardening of the parts. The conditions attributable to inflammation develop after birth, owing to the passage of fecal matter through this abnormally narrow channel, with subsequent irritation therefrom.

Embryology

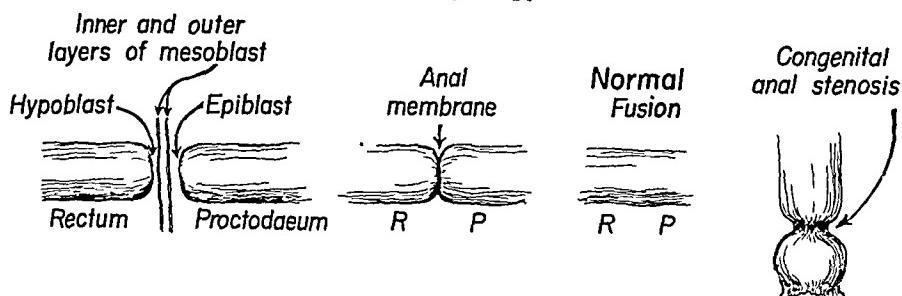


Fig. 1.—Schematic presentation of pertinent embryology in normal and abnormal fusion of rectum and proctodaeum.

Degrees of Anal Stricture

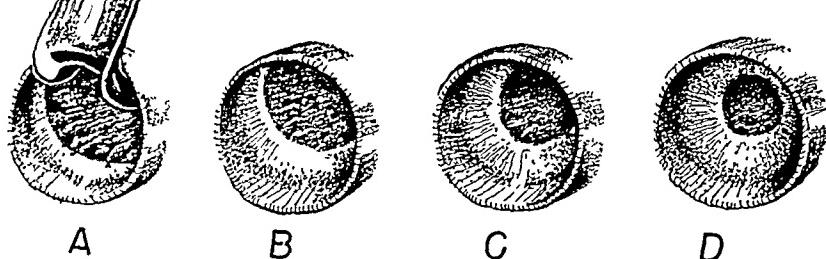


Fig. 2.—Schematic presentation of various degrees of congenital anal stricture.

Complications with Stricture

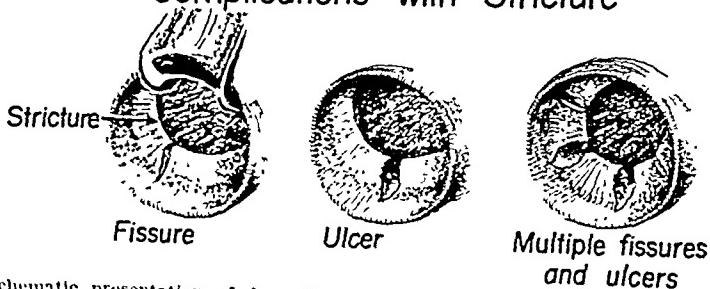


Fig. 3.—Schematic presentation of formation of fissures and ulcers secondary to congenital anal stricture.

The anal canal at birth ought to admit with comparative ease the little finger of a man's hand. When narrowing is pronounced one finds it difficult or impossible to introduce the finger through the contracted canal. These cases are the ones in which children are reported to have been constipated all their lives, and in which children frequently develop anal ulcers or fissures early in life due to tearing down of the stenosing tissue. Tuttle feels this condition should not be called stricture at the time of birth, because that term designates a pathologic narrowing of a canal which previously had been of normal proportions. It is true when these cases are treated later in life that the condition is one of stricture, referring, of course, to its origin and not to its pathology.

There can be no disagreement with Daniels' statement that "if one understands the fundamental steps in the evolution of the ano-rectum, one can almost visualize the various defects which might arise from arrested or faulty development as a result of imperfect obliteration of the proctodeal membrane." Crowell and Dulin state that "most anomalies are due to arrests or abnormalities of development arising in the 7th or 8th week of embryonic life. In the embryo of six weeks the cloaca is divided longitudinally by a down-growth of the uro-rectal septum. But for a time there is a small opening between the uro-genital tract and the hindgut, which is known as the cloacal duct. Failure of the cloacal duct to close accounts for the anomalous connections between the uro-genital tract and the rectum." Ladd and Gross state that "in the 22 mm. stage (late in the 7th week) a primary perineum is present. The perineum develops by the division of the cloacal membrane into the uro-genital membrane anteriorly and the anal membrane posteriorly, and by a down-growth and in-growth of the mesenchymal elements between these two membranes. Late in the 7th week, the uro-genital sinus has acquired an external opening, but the anal membrane does not rupture till later. A small dimpling of the anal pit forms the proctodeum, which in-pocketing continues until the proctodeum and rectum join their lumina by rupture of the anal membrane."

This phase of the embryology may appear clearer to some readers by Tuttle's terse description: "the epiblast of the proctodeum (embryonic anus) and the hypoblast of the hindgut approach each other, and on conjunction form a double septum. The absorption of the septum renders the conjunction of the anus and rectum complete, and leaves a narrow zone that indicates the transition from mucous to mucocutaneous tissue known as the pecten. This zone marks the lower limits of the rectum and the upper margin of the anus."

Congenital anal stenosis or stricture results from incomplete rupture of the membrane. Persistence of the membrane produces an imperforate anus.

Since most infants cry, have colic, and are more or less troubled with constipation or loose stools, these things are accepted for the most part as normal; and the parent, in consequence, does not go to the physician to have a rectal examination of the baby. Instead, nothing may be done, or else the formula may be changed, or suppositories, enemas, or cathartics given. And many times everything clears up quite well with such procedures. But when an infant at bowel movement continues to cry, draws up his legs, screams, and the stools

come out in a narrow, ribbonlike manner with evident signs of unusual straining or with a history of such constipation that might lead the physician to think he is dealing with a partial obstruction or Hirschsprung's disease, and when an older infant or young child similarly strains at bowel movements, cries, fears to go to the commode, has to be threatened or cajoled, or promised rewards, and may likewise have the type of constipation mentioned above, then certainly a rectal examination is in order. Often these little patients are dismissed by the general practitioner or pediatrician with a prescription for a suppository or change of diet; if this does not suffice, then in desperation laxatives or cathartics may be given. With negative results, the physician may discharge the patient as being pampered or of a neurotic type or he may vary the approach by saying the mother is overattentive and that either one or the other should see a psychiatrist. If the patient is not dismissed, the doctor will do a rectal examination and then find the anal canal narrowed: caused either by spasm due to an anal cryptitis, fissure, or ulcer, or else to a partially obstructing membrane of varying degree, the so-called congenital anal stricture or stenosis. The examination frequently reveals a fecal impaction above the narrowed zone. If a fissure or ulcer is found in conjunction with the stricture, the former is the result of a tearing down of the membrane secondary to pressure from straining during defecation, in an attempt to force the contents past the pathologically narrowed anorectum or anal canal. Most congenital strictures, unless found to be too thick, extensive, or unyielding, will clear up by means of dilatations. The stricture should be dilated daily with metal or gum elastic catheters, increasing the sizes to the point at which the little finger can be introduced. If, at the end of three to four weeks, considerable improvement is noted, then the parent is instructed to continue the procedure two to three times weekly up to six months. It is not always necessary to perform the dilatations daily, and many parents, after observing the procedure in the office a few times, are able to carry out the technique very well and capably at home, bringing the little patient to the doctor's office occasionally for check-ups in order to observe progress of the condition. If there is a concomitant superficial ulcer or fissure, it may be touched up with 10 per cent silver nitrate solution, which latter treatment is likewise sufficient for most superficial ulcers, fissures, or abrasions present in the absence of congenital anal stricture. If dilatations as outlined above afford little or no abatement of symptoms; or should the patient be in such a state that he cannot endure up to several months of dilatations, let alone the parents putting up with it, then it is advisable to resort to the following surgical procedure: effect multiple radial incisions of the stricture down to the external sphincter; free adhesions to the latter by running the points of a scissor between the sphincter and occluding membrane; and supplement postoperatively with dilatations twice weekly for two to three weeks. I would like to emphasize that in the technique I use no tissue is excised, and natural, painless movements occur in one or two days after the operation. Of the twenty-two cases of congenital anal stricture which I have seen in the past three years, eleven cleared up by dilatations, and the eleven which failed of such response were cured surgically by the method outlined. The patients referred who were subsequently operated upon had already

received the benefit of nonsurgical methods, with unsatisfactory results. Those sent for examination without prior treatment were always given a course of dilatations either by myself, the referring physician, or the parent, unless the extent of the condition did not warrant delay. Such cases as were improved by nonsurgical methods over a reasonable period of time never came to surgery. I would consider three to four weeks a reasonable length of time for nonsurgical treatment to indicate its worth. If little or no improvement is noted by the end of that period, continuing such methods for several months longer would hardly create any change for the better. The physician might be willing to continue further along this course, but not so the patient (who has very little to say in the matter), and surely not the parents, who have to put up with the infant or child at home.

CONCLUSION

Congenital anal stricture or stenosis is comparatively common, easy to recognize by digital examination of the anal canal, and just as easily missed because of failure to perform the examination. A rectal examination is always in order when the parent continues to tell the physician of the infant's or child's abnormal bowel habits. Owing to lack of reliable statistics inherent in the condition itself, one cannot state with any reasonable degree of accuracy the relative number of cases which clear up spontaneously, respond to nonsurgical methods, or are relieved only by surgery. Of twenty-two cases of congenital anal stricture seen by the author in the past three years, eleven, being resistant to non-surgical treatment, were satisfactorily eliminated by a simple surgical procedure.

REFERENCES

1. Daniels, E. A.: Rectal Disorders in Childhood. *Am. J. Dis. Child.* 54: 573-589, 1937.
2. Webb, C. H.: Congenital Malformations of the Anus and Rectum: Report of 162 Cases, *Am. J. Surg.* 23: 167-183, 1934.
3. Zahorsky, J.: Rectal Stenosis in Infancy, *Arch. Pediat.* 53: 187-190, 1936.
4. Tuttle, J. P.: A Treatise on Diseases of the Anus, Rectum, and Pelvic Colon, D. Appleton & Co., 1903, New York and London, p. 3, pp. 51-52.
5. Crowell, E. H., and Dulin, J. W.: Congenital Anomalies of the Anus and Rectum, *Surgery* 7: 529-539, 1940.
6. Ladd, W. E., and Gross, R. E.: Abdominal Surgery of Infancy and Childhood, Philadelphia and London, 1947, W. B. Saunders Co., pp. 167-168.
7. Idem: Congenital Malformations of the Anus and Rectum, *Am. J. Surg.* 23: 167-183, 1934.

TUBERCULIN PATCH TEST

FURTHER STUDY OF MODIFICATIONS OF THE NORMAL PROCEDURE

JOSEPH SCHWARTZMAN, M.D., AND MARION CERONE, R.N.
NEW YORK, N.Y.

IN A previous report,¹ it was shown that the efficiency of the tuberculin patch test was in direct proportion to the amount of autoclaving to which it was subjected, while all other variations attempted at that time had no deleterious effect.

In the present study, further attempts relative to variations in the method of applying the patch test were undertaken, among which were the following:

1. Keeping the patch for one and one-half years before testing.
2. Keeping the patch for four years before testing.
3. Keeping the patch for five years before testing.
4. Keeping the patch for five and one-half years before testing.
5. Keeping the patch for six years before testing.
6. Covering the patch with streptomycin solution (0.1 Gm. per cubic centimeter) and applying immediately.
7. Covering the patch with streptomycin solution (0.1 Gm. per cubic centimeter) for twenty-four hours and then applying.
8. Removing the patch after twenty-four hours.
9. Removing one patch after twenty-four hours and reapplying a second patch over the identical area.
10. Leaving the patch on for three days and then reading on the fourth day.
11. Leaving on the patch for four days and then reading on the fourth day.

As in the first report,¹ the patch sensitivity quotient (PSQ) was used to compare the sensitivity of each variation with the original patch test. In brief, this was arrived at by reading each test as varying from 1 to 4 plus; and then the sum of the regular patch readings was designated as the denominator and that of each variation as the numerator. A result of 1 or greater would indicate that there had been no deterrent effect, while any result less than 1 would indicate the degree of decreasing accuracy in doing the test under that given condition.

Listed in Table I is each of the eleven modifications, with each number corresponding to the variations as listed above.

From the Department of Pediatrics of the New York Medical College, Flower Fifth Avenue Hospital and Metropolitan Hospital.

TABLE I. EFFECT OF MODIFICATION ON PATCH SENSITIVITY

VARIATIONS	NO. OF TESTS DONE	PATCH SENSITIVITY QUOTIENT
1	7	.92
2	14	.75
3	4	.73
4	5	.80
5	7	.74
6	5	.95
7	5	.95
8	7	.94
9	7	1.50
10	6	1.00
11	6	1.12

In addition, it was decided to study the effect of elevated temperature of the patient on the patch test. Therefore, tests were done on the day of elevation of temperature and repeated when the temperature was normal for several days. Of twenty-three cases tested, twenty-one were negative and two were positive at the time of temperature and they remained so after the temperature was normal.

The effect of repeating patch tests on the same area in nontubercular infants was studied. As soon as one patch was removed, another was reapplied in the identical area. In eight cases, ten consecutive patch tests were performed in the above manner and all were negative. In two of the cases a dermatitis was noted in the region of the adhesive. In three of the cases patches were repeated in three and six months after the original testing and they persisted negative.

The effect of multiple or repeated patch tests on positive patch test cases was also reviewed. In this study, forty-three positive tuberculin cases were studied and the number of patch tests done varied from two to sixteen. In each case, at least two tests were done at one time and in twenty cases three were done simultaneously. In five others, four were done at one time and it was in one of the latter group that a reaction of temperature and generalized adenopathy was noted on the second day, and subsequently cleared up within one week. This gives a ratio of one reaction out of forty-three cases, or 2.3 per cent. These results are listed in Table II.

TABLE II. EFFECT OF REPEATED PATCH TESTS ON TUBERCULIN-POSITIVE CASES

NO. OF CASES	TOTAL NO. OF PATCHES PER CASE	NO. OF REACTIONS
18	2	0
15	3	0
3	4	0
2	6	1
2	7	0
1	10	0
1	11	0
1	16	0
Total 43		1 (2.3%)

DISCUSSION

Most of the modifications studied in this report were those that might be encountered in any hospital, clinic, or private physician's office.

It was noted that a great number of the patches that were one and one-half to six years old did not stick well and in those cases as well as any others demonstrating this defect, the patch was reinforced with new adhesive. Whenever there was a variation in the reaction of the two sides of the patch, the stronger reading was recorded. From the study it would seem that the age of the patch has some effect on the value of the test, since the PSQ dropped from 0.92 for those one and one-half years old to 0.75 for those four to six years old. Peculiarly enough, the results for the four- and six-year-old patches were almost identical.

Streptomycin in a dilution of 0.1 Gm. per cubic centimeter had practically no effect on the test, even when left in contact with the patch for twenty-four hours prior to its application.

Removal of the patch after twenty-four hours only affected the results very slightly, but reapplying another patch over the identical area accentuated the result. Removal of the patch later than the second day had no deleterious effect; if it was left on for four days and then read, the result was slightly accentuated. The presence of temperature did not appear to alter an individual's reaction to the patch.

Reapplying patch tests over the same area in nontubercular infants failed to produce any local sensitivity at the time, nor when repeated at three- and six-month intervals. This substantiates a previous study² in which patch tests were repeated every fourth day within a six-month period and no evidence of production of any sensitivity was detected.

Regarding reactions to the patch test, it was noted that out of forty-three tuberculin-positive children, only one developed a reaction; namely, temperature and adenopathy, after forty-eight hours. This cleared in one week. This reaction occurred in one of the cases that had had four patches applied at one time, which corresponded to our previous experience.¹ In the present study, the reaction was less than before, probably because fewer patch tests were done at one time. This would tend to caution one strongly against the use of multiple patch tests at any one time in a positive tuberculin case.

SUMMARY AND CONCLUSION

1. Fourteen modifications of the patch test were studied.
2. Patch test efficiency decreased with its age, being rapid at first and then more gradual.
3. Removal of a patch test after twenty-four hours lessened its accuracy slightly but reapplication of another patch in the same area or allowing the patch to remain on for four days resulted in an accentuation of the reaction.
4. Streptomycin applied locally over the patch had little to no effect.
5. Elevated temperature of the patient had no effect on the result of the test.
6. Repeated patch tests on nontubercular infants failed to stimulate any sensitivity.
7. Of forty-three tuberculin-positive children, a constitutional reaction occurred in one case (2.3 per cent) but cleared up quickly.

S. In conclusion, it can be stated that the patch test appears to be harmless to any nontubercular individual whereas in tuberculin-positive cases it should not be repeated unnecessarily, but more important yet is that multiple patch tests should be forbidden. Moreover, it would seem best to do the testing with patches that are not too old. If one were to be removed accidentally, re-application of another for twenty-four hours would definitely confirm the results.

REFERENCES

1. Schwartzman, J., Dragutsky, D., and Rook, G.: Tuberculin Patch Test, *J. PEDIAT.* 20: 50-53, 1942.
2. Schwartzman, J., Schneider, M., and Crusius, M. E.: Nonsensitization to Repeated Tuberculin Testing, *J. PEDIAT.* 33: 746-8, 1948.

LEPROSY, A DISEASE OF CHILDHOOD

WITH SPECIAL REFERENCE TO EARLY FINDINGS IN EYE, EAR, NOSE, AND THROAT
OF CHILDREN EXAMINED AT THE NATIONAL LEPROSARIUM AT CARVILLE, LA.

DAVID C. ELLIOTT, M.D.
CARVILLE, LA.

PEDIATRICIANS in the United States generally may be presumed to have had little opportunity to observe leprosy. Even in the endemic areas of this country they are likely to exclude it from their considerations, believing it to be a disease of adults. Physicians generally fail to realize that leprosy in all endemic areas of the world is continued principally through childhood infections. The histories of the majority of adult patients in this colony clearly indicate that their infections were well established before the age of 10 years, many having been admitted at the age of 5 years.

The eye, ear, nose, and throat manifestations of leprosy as seen in the children admitted to this hospital might be of value in distinguishing the protean rashes of leprosy from some of the childhood exanthemas and skin infections which leprosy often simulates. Before discussing these points of differential diagnosis it might be well to emphasize the importance of early diagnosis in all leprosy control programs. With the earlier recognition of leprosy children can benefit from treatment with the newer sulfone drugs and thus prevent the irreparable destructive complications of this insidious infection which might otherwise incapacitate them permanently.

SUSCEPTIBILITY OF CHILDREN

Muir¹ summarized the two generally accepted facts about leprosy in children when he stated that they are particularly susceptible to the disease and yet will not contract it if removed from the environment of the infectious parent at birth. Lara² believes that transmission by intrauterine means or breast feeding are doubtful questions but further observations are necessary before reaching conclusions. Both authors emphasize the danger in delaying the removal of the child from the infected home environment even for a few days. In a group of 260 leprous children of leprous parents, Lara found the first symptoms appearing in children under 5 years of age, manifest at approximately twenty months after exposure. Chiyuto,³ reporting an extensive experience in the Philippines, concludes that most evidence indicates leprosy is continued through the particular susceptibility of children under 3 years of age, and believes the disease will continue indefinitely unless young children are protected. Manalang,⁴ likewise experienced in the Philippines and Orient, emphasizes childhood as the period of infection and even goes so far as to deny vigorously the possibility of infection in adult life.

In this consensus on childhood infection we again refer to Chiyuto, who concludes that home isolation is inexpedient for many obvious reasons. He

believes that no eradication or control effort will succeed unless the intimate and prolonged contact between the known adult cases and infants is eliminated. He emphasizes an important point, frequently overlooked, that the discharged negative patient is potentially just as dangerous to the susceptible child as the positive case because of a possible relapse.

EARLY DIFFERENTIATING SYMPTOMS

In children and adolescents leprosy often runs a course which may simulate rubella. (It may be of interest that Webster's Dictionary gives the etymology of "measles" as synonymous with Middle English leprosy, for in that period leprosy was prevalent in England.) The febrile episode of leprosy is known simply as a lepra reaction. The elevation of temperature to 104° F. or higher, together with general malaise and a rash of small macules over the face and extremities, may closely approximate the course and appearance of measles. One confusing example is that of a Negro boy 12 years of age who was excluded from school with "measles." After this early rash and the febrile reaction continued for several weeks the patient developed nodules as seen in Fig. 1. These alone were present on admission to this hospital.



Fig. 1.—A Negro boy aged 12 years excluded from school with a diagnosis of "measles." Note the midarosis and edema of the nares. He lived in an endemic area (Texas).

There is no reference to leprosy in the family history. The mother died at the age of 30, and one brother and one sister died prior to the birth of this patient. All these deaths were from undetermined causes. In 1942 the boy was treated for "chicken pox." The distinguishing features of leprosy which might have been found on this boy even at that time are his ears, for the characteristic, full, pendulous lobes and the nodules on the auricle are indications that the disease has been long established. Likewise the swelling and tenderness about the tip of the nose and particularly the edema and infiltration about the alar

cartilages is almost pathognomonic. These indicators of nasal pathology together with a long-standing history of epistaxis, a very common symptom, should have led to an early inspection of the nasal cavity where the granulomatous mucous membrane over the nasal septum would have been found to be grossly infected with the characteristic acid-fast bacilli of Hansen.

These nasal symptoms are again demonstrated in Fig. 2 of a Negro boy admitted at the age of 11 years. The claim was made that the nodules on the hands and legs were of but three weeks' duration although he had multiple macules and induration of the face and brow. The family history is significant for his father was a patient at Carville.



Fig. 2.

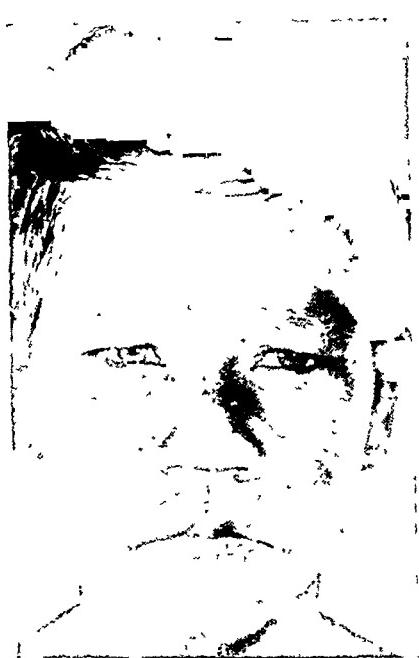


Fig. 3.

Fig. 2.—A Negro boy admitted aged 11 years, with a history of epistaxis, occlusion of nostrils, and edema of the tip, together with infiltration of the brow. His father has leprosy.

Fig. 3.—A white boy admitted aged 14 years, treated for "poison ivy" and "ringworm" for four years prior to the diagnosis of leprosy. Note the induration of face, edema of nose, and madarosis. He lived in an endemic area (Louisiana).

Madarosis is a finding which physicians can use in making a differential diagnosis. Our patient in Fig. 1 shows madarosis which was probably present even before the lepromatous lesions invaded the eyebrow. This loss of hair may include the lashes as well as the brow but is characteristically observed in the outer third or half of the eyebrow. It is generally bilateral. In the group of children in this study madarosis was seen in ten out of fourteen at the time of admission. It is our impression that when this condition exists leprosy has already been clinically active for as long as five years. Again in Fig. 3 madarosis is shown in a white boy admitted at the age of 14 years with

the advanced lepromatous form of the disease. The induration about the face, particularly about the eyes, nose, and ears, together with a lympho-edema of the extremities should have led earlier to a correct diagnosis. The eruption was first reported at the age of 10 years. The edema, together with the rash, misled the physicians, who treated the case at first as "poison ivy." As only a slight degree of success followed the local therapeutic measures and macules appeared, the diagnosis was changed to "ringworm." This boy had advanced nasal findings with a history of many attacks of epistaxis during the previous four-year period. A school physician commented upon his extremely enlarged tonsils, which probably showed a tenacious semiplastic material plugging the tonsillar crypts. This material was not caseous and was not expressed from the tonsils. A tonsillectomy was performed with a resulting exacerbation of all of the skin lesions. After a febrile period of a few weeks with no change in the macular eruption and general edema, a diagnosis of leprosy was made. This boy's family history, as reported, is negative to date, although he has resided in an endemic area since birth.



Fig. 4.—A Negro boy, admitted at the age of 11 years with a history of leprous lesions since the age of 3 years. Note the edema at the tip of the nose, induration of the brow, and nodules on the face. The mother and maternal grandmother have leprosy.

These characteristic changes of the loss of hair in the external margins of the brow and the induration in the face with the edema about the nose are again shown in Fig. 4. This Negro child admitted at the age of 5 years had a history of many episodes of rhinitis, epistaxis, and a macular eruption over the face and body since the age of 3 years. His mother is a patient in this hospital and his maternal grandmother died here. This family history, incidentally, shows the relentless continuance of leprosy through generation after generation when no control program exists to remove children from the infected environment immediately at birth.

There seems to be little pathology of the ear except for the characteristic skin lesions over the auricle and the large, pendulous lobes developing as the disease becomes established. We have not seen hyperesthesia or anaesthesia of the external ear, nor have the children shown any thickening of the great postauricular nerve. There has been no nerve deafness in the group and only one child, a Mexican girl of 14 years, showed otitis media. This girl, though not admitted until recently, has had leprosy since the age of 5 years, her early lesions being of the lazarine, sharply circumscribed, hemorrhagic-necrotic type resulting in deep scarring. Oddly enough no loss of cilia or brow hair was observed. She showed advanced lepromous changes in the auricle. Her ocular findings, however, were of special interest.

The conjunctiva were free of disease and there was no evidence laterally at the limbus of the episcleritis so often seen in patients who have had leprosy for more than ten years. On slit-lamp examination this girl showed the characteristic beading of the corneal nerves. Twelve of the fourteen children showed this phenomenon in each eye and a thirteenth showed it in the right eye only. These points of brilliance stand out on the shaft of the corneal nerves and seem to be an infiltration along the sheath representing *in vivo* and in miniature the infiltration of the peripheral nerves commonly seen in the more advanced stages of the disease. This beading is characteristically found in the corneal nerves of the superior and temporal quadrant, usually bilaterally. It is our belief that these findings indicate that the infection has been present for about ten years because the average age of this group is 11 years and the established diagnosis dates range from 3 months to 10 years prior to admission. This infiltration may be the only finding in an otherwise healthy cornea.

A punctate keratitis develops in these same areas of the cornea and is usually bilateral, following a symmetrical pattern in the superior temporal quadrants. It was found, however, in only six of the children in the group when studied with the slit-lamp. In young adults and more advanced cases the punctate keratitis together with an interstitial keratitis may be seen in these same areas but probably not before the disease has been established for fifteen or twenty years. The six children showing a nebulous microkeratitis in the substantia propria in the vicinity of the damaged corneal nerves had an average age of just over 13 years, the youngest being 11, the eldest 14 years old. All had the lepromatous form of the disease.

A vascular change at the limbus which is quite characteristic and which may be referred to as lepromous neovascularization was found in eleven of the fourteen children. This is first recorded by Vale⁷ in his work *Subsidiary Studies of Leprosy of the Eye*. Vale believes this vascularization may appear as a benign manifestation before any dermatologic symptom of leprosy exists. With the corneal microscope these capillaries can be seen to drain from deep within the cornea a rapid flow of blood and they unite over the limbus to form a large vessel concentric with and upon the corneal scleral junction. This again is laterally and along the superior temporal quadrant where this vessel

can often be seen with the naked eye. This leprous pattern is quite different from the normal radially disposed capillaries at the limbus.

An additional slit-lamp observation in this group of children is the frequent occurrence of filaments in the anterior chamber. These arise from the surface of the iris but should not be confounded with remnants of a persistent embryonic pupillary membrane. In eight of the fourteen children these filaments, generally incorporating particles of pigment, were found in the anterior chambers in many fantastic patterns. They were sometimes attached to the posterior surface of the cornea or might loop across the pupil to the opposite margin of the iris. Their attachments seem to be upturned sections of the mesodermic layer of the iris frequently rolled back for some distance along the margin of the pupil or punched out in moth-eaten patterns. Some eyes showed pedunculated free ends of this iris tissue waving like hydra in the aqueous. This finding occurred in about 60 per cent of the children studied, and is, we believe, a complication seen within the first few years of infection, for it was a prominent finding in a child 4 years old.

In none of the children have we observed the "pearl" formations of leprous iritis which are commonly seen in adults with a lepromatous form of the disease. The one possible exception to this was the 14-year-old girl who has had leprosy since the age of 5 years, but has had no sulfone treatment. In the extensive network of filaments in her right eye there are small semi-gelatinous masses on the iris at the point of attachment of the filaments. These are neither waxy nor white, yet in form are similar to the discrete "pearls" of leprous iritis seen in more advanced cases. This child likewise showed the only evidence in the group of serious involvement of the lens. On the posterior surface of the lens of the left eye there was seen with the spot beam of the slit-lamp a cluster of small, white nodules similar to those observed in leprous iritis. In three other children the only changes on the lens were particles and granules of pigment which were not remarkable. In none of the children was there any impairment of normal visual acuity.

Normal fundi were found on ophthalmoscopic examination in twelve of the fourteen. However, in a female white child 4 years of age a distinct patch of choroiditis approximately 3 mm. in diameter was noted nasally in the left eye. In a similar area and again in the left eye a patch of choroiditis was seen in a white boy of 13 years. This is considered by some writers as a sign of latent leprosy.⁸ It is interesting that this 4-year-old child presenting the choroiditis had a most lavish display of wisps and filaments in her right eye only, but she showed beaded corneal nerves in each superior temporal quadrant and an extensive epicorneal vascular network in these areas. Dermatologically she had but one maculelike area which did not show bacilli in the biopsy, but which histologically was reported as leprous in character. This rather well illustrates Chiyuto's⁹ contention that it is an error to depend exclusively upon the demonstration of acid-fast bacilli for the establishment of the diagnosis to the exclusion of clinical-pathological findings and a family

history that is positive. This child's mother has moderately advanced, lepromatous leprosy.

CONCLUSIONS

We wish to stress the importance of early diagnosis as an essential feature of any public health approach to the control of leprosy, and to emphasize the need for disseminating to all physicians in endemic areas medical information upon the earliest symptoms of leprosy, particularly in children. While the ultimate control of leprosy undoubtedly involves the removal of children at birth from the infectious environment, clinicians interested in the individual child must be more familiar with the disease in order to give their patients the benefits which may accrue from early treatment with the sulfone drugs.

Our findings and observations are limited to the small group of fourteen children admitted to the National Leprosarium in the last two years, and cannot, therefore, compare with the observations of other workers in those parts of the world where the truly early manifestations of leprosy in infants and children under 3 years of age can be studied. It might be misleading to assume from our limited illustrations that leprosy in the children of the United States is restricted to boys and is predominantly in the Negro. This is not the case, for in this group of fourteen children there were eleven boys, six being white, and all three of the girls were white. The fact that so few girls are admitted to this hospital rather indicates the widespread practice of retaining girls within the family until such time as the extensive complications of the disease compel the family to seek complete hospital care. Most writers report in the Philippines the infection rate in children under 5 years of age as being the same for both sexes.

In a differential diagnosis of leprosy from other chronic skin diseases or some of the common exanthemata of children an ophthalmological study is of considerable value. Even without access to such consultations the pediatrician and general practitioner in areas where leprosy is endemic should become more familiar with the common and characteristic external manifestations of this disease, particularly as seen in the eyebrows, ears, the eye, and the nose. In addition they should remember that in families where a case of leprosy is known to exist all younger members should be carefully scrutinized and observed for a period of years as the incubation period of leprosy is unknown, extending in some cases to a period of twenty years.

Although intensive therapy with the sulfone derivatives may be of great benefit to the individual child, it should be emphasized again that treatment alone will not by any means prevent the spread of this disease. As Muir⁶ emphatically states, leprosy would die out of an endemic area within two generations if all children were kept free from contact with either known positive cases or so-called negative-discharged patients.

SUMMARY

1. An abstract of prevailing opinion concerning the special susceptibility of children to leprosy emphasizes the continuation of this disease primarily as a disease of childhood.

2. The diagnostic features and distinguishing characteristics of leprous lesions about the eyes, ears, nose, and throat with which the physician should become familiar are cited with illustrations and case reports.

3. In endemic areas in the United States leprosy appears to be a disease of childhood generally acquired before the age of 5 years.

4. If erroneously diagnosed or if recognized but hidden in the family, these cases may be foes for exposing other children in the community.

REFERENCES

1. Muir, E.: Manual of Leprosy, Baltimore, 1948, Williams & Wilkins Company, p. 6.
2. Lara, Thomas C. N., Cazabiro, B., and Nolasco, J. O.: Leprosy in Infancy and Childhood, Internat. J. Leprosy 6: 277, 1948.
3. Chiyuto, Sulpicio: Leprosy Control Based on Transmission, Susceptibility and Pathogenesis, Monthly Bull. Bureau Health (Manila) 24: 3-15, 1948.
4. Manalang, Cristobal: Transmission of Leprosy, Monthly Bull. Bureau Health (Manila) 24: 1948, Reprint No. 4523.
5. Chiyuto, Sulpicio: Reorientation of the Control of Leprosy With Emphasis on Infantile Susceptibility, Monthly Bull. Bureau Health (Manila) 24: 1948.
6. Muir, E.: Manual of Leprosy, Baltimore, 1948, Williams & Wilkins Company, p. 179.
7. Vale, Sergio: Subsidiary Studies to Leprosy of the Eye, Imprensa Nacional, Rio de Janeiro, Brazil, 1946, p. 46.
8. Duke Elder, Sir Stewart: Textbook of Ophthalmology, Vol. III, St. Louis, 1942, The C. V. Mosby Company, p. 2322.

POTASSIUM BROMATE POISONING

WILLIAM KITTO, M.D., AND KENNETH W. DUMARS, M.D.
DENVER, COLO.

THE effects of ingestion of bromates on man have received little attention in the medical literature. Two fatalities with severe kidney damage have been reported.^{1, 2} It is the purpose of this paper to report three patients showing varying degrees of toxicity due to ingestion of potassium bromate. The first showed severe toxic nephrosis with anuria, the second mild renal irritation with oliguria, and the third gastrointestinal irritation with no evidence of kidney damage.

CASE REPORTS

CASE 1.—E. W., a 3-year-old white male child, was admitted to the pediatric service of Colorado General Hospital on June 11, 1947. Six days prior to admission he had ingested an undetermined quantity of permanent wave solution neutralizer, followed by vomiting, diarrhea, and virtually complete anuria. He had not been febrile. On the day of admission his parents noted that his face appeared puffy. His past history and family history were noncontributory.

The physical examination was normal except that the child appeared slightly ashen, hyperpneic, and his face was puffy. No pitting edema was present. Laboratory findings on the day of admission were as follows: blood sugar 205, nonprotein nitrogen 225, urea nitrogen 170, creatinine 25 (all figures represent milligrams per 100 c.c. of whole blood). Serum chlorides were 89 meq. per liter, and serum carbon dioxide was 6.7 meq. per liter. Hemoglobin was 10.2 Gm.; red blood cells, 3,780,000; white blood cells 7,200. Analysis of the initial urine obtained on June 13 showed 2 plus albumin, a trace of acetone, and some degenerated, granular casts.

Treatment consisted of peritoneal lavage and parenteral fluid administration. Kidney function returned rapidly after the third day of hospitalization.³ Before discharge, July 12, 1947, analysis of urine revealed normal findings. A concentration test showed a maximum specific gravity of 1.015, and phenolsulphon-thalein test showed 40 per cent excretion. The blood sugar was 114 mg. per 100 c.c.; nonprotein nitrogen, 39 mg. per 100 c.c.; and carbon dioxide, 23.4 meq. per liter. Mantoux test was positive in dilution of 1:10,000. X-rays of the chest and abdomen were normal.

The child was followed in the Pediatric Outpatient Department from August, 1947, to November, 1947. No signs referable to kidney or liver damage were noted. His nonprotein nitrogen on one determination was 36 mg. per 100 c.c. No urines revealed greater concentration than that recorded before his discharge from the hospital. Follow-up chest x-rays showed development of a primary tuberculous complex.

From the Pediatric Service of the University of Colorado Medical Center and the Denver General Hospital.

CASE 2.—D. B. This 2½-year-old white female child was admitted to Denver General Hospital March 7, 1948, approximately forty-five minutes after having ingested one-third cup of home permanent wave neutralizer solution. The child's mother had discovered the accident immediately and had given the child a mixture of raw eggs and milk, which had been vomited promptly. She had repeated this, and the child had repeated emeses prior to her admission to the Emergency Ward at Denver General Hospital, where she received gastric lavage. Past and family histories were noncontributory.

Physical examination at the time of admission revealed an acutely ill, semi-lethargic, retching white female child with slight abdominal distension. No other abnormal physical findings were apparent. The child was given a hypodermoclysis of 5 per cent glucose in distilled water and allowed to take milk and lactate-Ringer's solution to tolerance every three hours. She retained very little oral fluid and was started on intravenous fluids the following morning and maintained on parenteral fluids for the succeeding forty-eight hours.

During the first forty-eight hours of hospitalization the child was almost anuric, voiding only 70 to 100 c.c. of urine, which was not abnormal except for occasional pus cells, and which had a specific gravity of 1.020. Her initial blood chemistries showed nonprotein nitrogen to be 71 mg. per 100 c.c.; serum carbon dioxide was 17.9 meq. per liter. The mild acidosis was corrected by means of ½ molar sodium lactate.

The child's urinary output rapidly increased after the third hospital day. The urine obtained on the fourth hospital day revealed innumerable red blood cells and pus cells. No red blood cells were found in the urine after the seventh hospital day. A culture of urine on the eleventh hospital day revealed the presence of *Escherichia coli*, which rapidly disappeared after treatment with streptomycin.

The child was discharged on the twentieth hospital day. She was readmitted on May 4, 1948, for evaluation of possible kidney damage. Repeated urine analyses, blood chemistries, and an intravenous pyelogram were normal at this time.

CASE 3.—N. C. This 3-year-old white female was admitted to Pediatric Service, Denver General Hospital, Dec. 6, 1948, with a history of having ingested two to three ounces of permanent wave neutralizer solution approximately thirty minutes before admission.

Physical examination at the time of admission revealed no abnormal findings. She was given gastric lavage on admission and 300 c.c. of normal saline solution followed by 500 c.c. 5 per cent glucose in distilled water intravenously. Urine analyses and other laboratory examinations were within normal limits. The child exhibited some vomiting following gastric lavage and appeared slightly lethargic throughout the first thirty-six hours. She voided freely during this time. No other toxic manifestations were seen through the four-day period of hospitalization.

COMMENT

The neutralizer supplied with home permanent wave sets consists of the bromate of either sodium or potassium, more frequently the latter. This is

supplied as a powder which is dissolved in water to make a solution containing 9 Gm. salt per pint of water. If this solution is prepared when the wave solution is applied, then allowed to stand within the reach of small children for hours, it constitutes a hazard. Despite a somewhat bitter taste, solutions left about in teacups are inviting to the run-about child, and in the usual dilution are not sufficiently irritating to the gastric mucosa to cause immediate vomiting.⁷

Little is written regarding the effect of potassium bromate. Experimentally it produces vomiting, diarrhea, central nervous system symptoms (apathy and convulsions), hemolysis, and renal damage. At necropsy dogs who have been subjected to sodium bromate poisoning show hyperemia, bleeding and erosion of the gastric mucosa, and denudation of the esophagus. Renal changes include hyperemia, parenchymal bleeding, and epithelial degeneration which is most marked in the ascending portion of the loop of Henle.⁴ Januschke and Inaba⁵ report that subcutaneous injections of sodium bromate produce methemoglobinemia in guinea pigs, but this has not been confirmed by other workers.⁶ Autopsy material shows severe kidney tubular damage to be a most prominent finding. Necrosis of hepatic cord cells and transverse fragmentation of cardiac muscle fibers are seen.¹

The three cases reported, together with the fatal cases from the literature,^{1, 2} show a range of effects of potassium bromate poisoning in man, varying from gastric irritation without evidence of kidney damage (Case 3), oliguria (Case 2), anuria (Case 1), to fatal termination with toxic nephrosis.^{1, 2}

Gastrointestinal effects of potassium bromate depend on the caustic action of hydrobromic acid and free bromine, which are produced by a reaction of bromate and hydrochloric acid in the stomach. The renal damage is due in part to the products of hemolysis and in part to the oxidizing effects of bromate ion of the renal tubules.^{4, 6} The first patient showed only a mild degree of anemia, and though no tests for bilirubinemia were made, it is doubtful that hemolysis was an important factor in the production of his anuria.

In the three cases presented central nervous symptoms were not prominent. Some gastrointestinal symptoms were present in all three cases. One child demonstrated no kidney damage while the other two exhibited varying degrees of kidney damage.

The increasing popularity of home permanent waves makes probable an increasing frequency of poisoning with potassium bromate in small children. We have no suggestions for treatment other than that it should be symptomatic and that a mild reducing agent such as activated charcoal or dilute sodium thiosulfate solution should be used in performing gastric lavage. Bromate ions are rapidly reduced after absorption,⁷ and a test for bromate is of no value in determining the toxic agent; however, low levels of bromide do appear in the blood stream, and may be of confirmatory value in establishing a diagnosis. Although no bromide determinations were made on the three patients reported, we have recently seen a fourth patient who, following ingestion of approximately two ounces of cold wave neutralizer solution, showed a blood bromide level of 75 mg. per 100 c.c. The course of this 8-year-old boy was almost identical with that reported for the third patient.

SUMMARY

1. Three cases of poisoning due to ingestion of potassium bromate are presented.
2. These cases illustrate a range of effects of toxic action of potassium bromate, varying from moderate gastrointestinal irritation to severe toxic nephrosis.
3. A review of experimental data on the effects of potassium and sodium bromate is presented.

REFERENCES

1. Dunsky, Irvin: Potassium Bromate Poisoning, *Am. J. Dis. Child.* **74**: 730, 1947.
2. Carratalá, R., and Urcaray, L.: Grave Intoxication Due to Ingestion of Potassium Bromate, *Rev. Assoc. med. argent.* **55**: 529, 1941.
3. Swan, H., and Gordon, H. H.: Peritoneal Lavage in the Treatment of Anuria in Children, *Pediatrics*. In press.
4. Rost, E.: *Handbuch Der Experimentellen Pharmacologie* **3**: 387, edited by A. Heffter, Berlin, Verlag von Julius Springer, 1927.
5. Januschke and Inaba, *Ztschr. f. d. ges. exper. Med.* **1**: 141, 1913. (Quoted by Rost.⁴)
6. Sollman, T.: *A Manual of Pharmacology and Its Applications to Pharmacology and Toxicology*, ed. 2, Philadelphia, 1922, W. B. Saunders Company.
7. Mulinos, M. G.: Personal communication.

FEEDING PREMATURE INFANTS

COMPARISON OF FOUR GROUPS OF PREMATURE INFANTS FED DIFFERENT MILK MIXTURES

JAMES W. BRUCE, M.D., LOUIS J. HACKETT, JR., M.D., AND
JOHN E. BICKEL, M.D.
LOUISVILLE, KY.

EVER since the emergence of pediatrics as a specialty, human breast milk has been considered the sine qua non for feeding premature babies. Investigations in the past few years, however, have thrown doubt on the unquestioned supremacy of mother's milk in this field.¹⁻³ It was thought that further work comparing the growth and well-being of premature babies fed human breast milk with those fed various cow's milk mixtures would be valuable.

It is recognized that premature infants do not handle cow's milk fat as well as some other fats.⁴⁻⁶ For this reason mixtures low in butter fat content or those in which cow's milk fat was supplanted by olive oil, corn oil, and other fats were used. Also, since premature infants are known to have low serum proteins for the first few months of life,⁷ it is generally believed that prematures do better when higher protein feedings are used than are obtained in human breast milk.

MATERIAL

From Sept. 1, 1947, to Aug. 31, 1948, there were 192 premature infants born at the Louisville General Hospital. Of these, ninety-one were not suitable for our study because they either survived less than forty-eight hours or were hospitalized for too short a time to make a study profitable. The remaining 101 babies comprised the material for our study. These infants were, at birth, assigned in rotation to one of four groups, A, B, C, or D. Infants weighing less than 1,750 Gm. at birth were assigned in a separate rotation so that all groups would have a comparable number of small infants.

Group A consisted of thirty infants; twenty-four weighed more than 1,750 Gm. at birth and six weighed less than 1,750 Gm. All of these babies received a mixture of three parts human breast milk to one part of skimmed lactic acid milk. This feeding contained approximately 6.5 per cent carbohydrate, 2.8 per cent fat, and 2 per cent protein, and had a caloric value of approximately 0.61 Calorie per cubic centimeter (see Table I).

Group B consisted of twenty-six infants; twenty weighed more than 1,750 Gm. at birth and six weighed less than 1,750 Gm. These infants received a powdered, modified cow's milk preparation (Similac*), in which part of the cow's milk fat was replaced by olive, coconut, and corn oil. This feeding contained approximately 6.8 per cent carbohydrate, 3.4 per cent fat, and 1.5 per cent protein, and had a caloric value of 0.7 Calorie per cubic centimeter.

Group C consisted of twenty-two infants; sixteen weighed more than 1,750 Gm. at birth and six weighed less than 1,750 Gm. This group received a feed-

*From the Department of Pediatrics, University of Louisville School of Medicine.

ing mixture of the powdered, modified cow's milk, as described above (Similac*), with added casein hydrolysate (Protolysate†). This mixture contained approximately 68 per cent carbohydrate, 34 per cent fat, and 55 per cent protein, and had a caloric value of approximately 0.86 Calorie per cubic centimeter.

TABLE I PREPARATION AND COMPOSITION OF FEEDINGS USED

GROUP	METHOD OF PREPARATION OF EACH 100 C.C.	APPROXIMATE PER CENTAGES			CAL- ORIC VALUE PER C.C.	% CALORIES OBTAINED FROM EACH COMPONENT
		CARBO- HYDRATE	FAT	PRO- TEIN		
A	Breast milk	75 c.c.				Carbohydrate 44.1
	Skimmed lacteal acid milk	25 c.c.	6.5	2.8	0.61	Fat 42.5
B	Powdered modified cow's milk	12.5 Gm	6.8	3.4	0.70	Protein 13.4
	Water to make	100 c.c.		1.5		Carbohydrate 42.6
C	Powdered modified cow's milk	12.5 Gm	6.8	3.4	0.86	Fat 48.0
	Casein hydrolysate	1.0 Gm		5.5		Protein 9.4
D	Water to make	100 c.c.				Carbohydrate 34.2
	Powdered half-skimmed cow's milk	14.2 Gm	5.8	1.5	0.61	Fat 25.4
	Water to make	100 c.c.		4.1		Protein 30.9

Group D consisted of twenty three infants, fifteen weighed more than 1,750 Gm. at birth and eight weighed less than 1,750 Gm. These infants received a powdered, half-skimmed cow's milk preparation (Alacta‡), which provided approximately 58 per cent carbohydrate, 15 per cent fat, and 41 per cent protein, and had a caloric value of approximately 0.61 Calorie per cubic centimeter.

METHOD

For the first twelve hours of life, sometimes longer in the case of very small infants, all prematures received nothing by mouth. During the next twelve hours all received feedings of 5 per cent glucose solution. For the second twenty-four-hour period dilute feeding mixtures A, B, C, and D were given to the respective groups. Usually after forty-eight hours mixtures A, B, C, and D were given in undiluted form. A three-hour feeding schedule was maintained uniformly. No attempt was made to standardize the caloric intake in terms of body weight. Rather, depending upon each infant's appetite, the least amount of the mixture which would produce a perceptible weight gain, and at the same time satisfy the infant's hunger, was ordered. Feedings were increased by 3 to 5 c.c. per feeding per day only when a baby's hunger or failure to gain weight demanded it. Almost all infants were given feedings by bottle through a soft rubber "premature" nipple. No feedings were forced, but a few infants too weak to nurse were fed by gavage.

*The Similac used in this study was furnished through the courtesy of M and R Dietetic Laboratories, Inc.

†The Protolysate used in this study was furnished through the courtesy of the Mead Johnson Company.

‡The Alacta used in this study was furnished through the courtesy of the Mead Johnson Company.

After the first seven days all infants received daily vitamin supplements of 5,000 U.S.P. units of Vitamin A, 1,000 U.S.P. units of Vitamin D, and 50 mg. of ascorbic acid. At the end of the second week the daily administration of 0.16 Gm. of ferrous sulfate was begun.

Each group of infants received identical routine premature nursing care until discharged from the hospital. All babies weighed at least 2,500 Gm. when dismissed. Some babies whose poor home conditions demanded that we keep them in the hospital for a longer time weighed considerably more.

At the termination of the period of study, the average age when birth weight was regained, the average mean weight gain in grams per kilogram of body weight per day from the eighth to the eighteenth day of life, and the average length of hospital stay were determined for each group and these results were compared.

RESULTS

Results of this study are recorded in detail in Table II.

Deaths.—Five of the 101 infants studied died during their hospital stay. None of the deaths were directly attributable to the type of feeding received. There were no deaths in Group A. One infant in Group B, birth weight 1,176 Gm. died on the thirty-eighth hospital day after a thirty-hour course of fulminant diarrhea of unknown cause. Two infants in Group C died. One, weighing 2,126 Gm. at birth, died on the fifteenth hospital day after a steadily downhill course marked by persistent vomiting. The other death in this group occurred in an infant weighing 1,290 Gm. at birth. Moderate jaundice and macroglossia were the only significant findings prior to death on the seventeenth day. There were two deaths in Group D. One infant, weighing 1,569 Gm. at birth, died of bronchopneumonia on the fortieth hospital day after a stormy course during which vomiting was the outstanding symptom. The second death in this group occurred on the forty-sixth hospital day in an infant weighing 2,268 Gm. at birth. Post-mortem examination revealed an interventricular septal defect, bronchopneumonia, and atelectasis.

Age Birth Weight Regained.—The infants fed the powdered, modified cow's milk preparation, Group B, regained their birth weight more rapidly than did the infants fed the other milk mixtures. An average of 14.7 days was required for these infants to regain their birth weights, as compared to 21.6 days required for the infants fed the human breast milk mixture, Group A; 17.2 days for the infants fed powdered, modified cow's milk with added casein hydrolysate, Group C; and 20.2 days for the infants fed the powdered, half-skimmed cow's milk preparation, Group D. The over-all average length of time required to regain birth weight was 18.7 days. This time is somewhat longer than that reported by other authors.^{8, 9}

Daily Weight Gain.—The mean average daily weight gain in grams per kilogram of body weight from the eighth to the eighteenth day for the entire group was 6.5 Gm. Infants in Group A and B were above average in this regard, gaining 7.3 Gm. per kilogram per day and 8.3 Gm. per kilogram per day, respectively. Groups C and D were somewhat less than average, gaining 5.6 Gm.

TABLE II. MATERIAL AND RESULTS

	GROUP A			GROUP B			GROUP C			GROUP D			TOTAL			AVG. GROUPS		
	BIRTH WEIGHT OVER 1,750 GM.	BIRTH WEIGHT OVER 1,750 GM.	TOTAL OR OVER 1,750 GM.	BIRTH WEIGHT OVER 1,750 GM.	BIRTH WEIGHT OVER 1,750 GM.													
	Males	Females		Group I	Group II													
Total number	2 ^t	6	17	17	16	16	16	16	16	15	15	11	11	11	9	14	17	
Average birth weight (gm.)	2,123	1,536	2,006	2,100	1,467	1,951	2,110	1,518	1,965	2,117	1,529	1,926	2,123	1,514	1,906	1,750	1,750	1,750
Average age when birth weight regained (days)	19.3	21.4	21.6	14.5	15.2	14.7	15.0	22.6	17.2	20.0	20.7	20.2	20.7	20.2	17.3	21.0	18.7	
Average mean weight gain in grams per kilo grams per day	7.5	6.3	7.3	7.7	10.4	8.3	7.3	0.7	5.6	3.8	5.6	4.5	6.7	6.1	6.6	6.5	10.1	
Average length of hospital stay in days	32.9	56.0	38.3	30.2	53.2	35.5	26.1	51.5	33.0	35.2	54.0	41.7	30.7	35.8	37.2	32	32	32
Vomiting	1	1	1	1	1	1	1	1	1	1	1	1	3	3	11	11	11	11
Diarrhea	1	1	1	1	1	1	1	1	1	1	1	1	3	3	9	9	9	9
Deaths	0	1	1	1	1	1	1	1	1	1	1	1	3	3	5	5	5	5

per kilogram per day and 4.5 Gm. per kilogram per day, respectively. Our results here are not comparable with those of other authors, since we used for study a period a little earlier in life than is usually used. We did this, however, to enable us to study a number of infants who otherwise could not have been included.

Hospital Stay.—The average length of hospital stay was shortest, thirty-three days, for the group of infants fed powdered, modified cow's milk with added casein hydrolysate, Group C, and was longest, 41.7 days, for the group fed half-skimmed cow's milk, Group D. The group fed the human breast milk plus skimmed lactic acid milk mixture, Group A, had an average hospital stay of 38.3 days, while the group fed powdered, modified cow's milk alone, Group B, remained in the hospital an average of 35.5 days. These periods of hospitalization are a little longer than those reported by various authors as quoted by Wallace, Baumgartner, and Park.¹⁰

Complications.—Vomiting sufficiently severe to mention occurred in one infant in Group A, two in Group B, five in Group C, and three in Group D. Diarrhea of more than one day's duration occurred in one infant in Group A, one in Group B, four in Group C, and three in Group D.

COMMENTS

To evaluate the results of this study one must bear in mind the fact that these premature babies were not given isocaloric amounts of the various feedings used. On the contrary, a modified self-demand regime permitted each baby to take or refuse whatever amount he chose. Therefore, our results indicate not only the possible advantages of one feeding mixture over another in terms of composition and nutritional efficiency, but also compare some of the ill-defined, but quite important qualities such as acceptability. For example, even though the infants in Group C had the shortest hospital stay, the length of time required for these infants to regain their birth weight and the mean average daily weight gain in the early days were less than for those infants in Group B, because it was found that the very young prematures more readily accepted mixture B, whereas they often refused considerable amounts of mixture C until they were several weeks of age.

The differences noted in the various groups in our study are probably of some statistical significance, but are of far less practical significance. For example, it is impossible to determine by examination at the time of dismissal which infants had any one of the various feedings. Further, it does not necessarily follow that the more rapidly growing babies are the better babies. Lastly, in a study of this nature, it is extremely difficult to say just what part the feeding variations had to play in producing the statistical differences noted.

We do not intend to imply, as a result of the study of such a small number of prematures, that all premature babies should be fed on a modified self-demand basis, nor that any one of the milk mixtures used in this study is necessarily ideal for feeding premature infants. More important is the realization that, given an adequate physical set-up and a trained and interested

nursing staff, practically all of the currently used human breast milk mixtures, as well as cow's milk mixtures, different as they may be in composition and calorie value, accomplish the prime purpose of safely bringing an infant from the stage of prematurity to a level of relative maturity without nutritional deficiency. The speed with which this is done may vary depending upon the feeding used, and often speed is important in terms of reducing the cost of hospital care. Bear in mind, however, the fact that the premature infant himself is not at all interested in the rapidity with which the steps in his development are accomplished. So, although we may at times hurry the premature's course, it is just possible that a happier, equally healthy baby may attain his relative maturity if allowed to proceed at his own rate of growth on a feeding mixture that he readily accepts.

CONCLUSIONS

1. Premature infants do as well or better when fed cow's milk preparations as when fed human breast milk mixtures.
2. Differences noted in the group studied may be more apparent than real and may not necessarily be due to the differences in the feedings given.

SUMMARY

1. A group of 101 premature infants born at Louisville General Hospital from Sept. 1, 1947, to Aug. 31, 1948, were assigned in rotation to one of four groups. Each group received a different milk mixture. All of these infants were fed on a modified self-demand basis.

2. Determinations of the average age when birth weight was regained, the average mean weight gain in grams per kilogram of body weight per day from the eighth to the eighteenth day, and the average length of hospital stay were made for each group at the termination of the period of study.

3. The results were then compared and briefly discussed.

REFERENCES

1. Gordon, H. H., Levine, S. Z., and McNamara, H.: Feeding of Premature Infants, *Am. J. Dis. Child.* 73: 442, 1947.
2. Lawrence, J. M., Herrington, B. L., and Maynard, L. A.: Human Milk Studies: XXVII, Comparative Values of Bovine and Human Milks in Infant Feeding, *Am. J. Dis. Child.* 70: 193, 1945.
3. Powers, Grover F.: Some Observations on the Feeding of Premature Infants, Based on Twenty Years Experience at the New Haven Hospital, *Pediatrics* 1: 145, 1948.
4. Holt, L. E., Jr., Tidwell, H. C., Kirk, C. M., Cross, D. M., and Neale, S.: Studies in Fat Metabolism I. Fat Absorption in Normal Infants, *J. PEDIAT.* 6: 427, 1935.
5. Ladd, M.: Homogenized Olive Oil and Fat-Free Milk Mixtures in Case of Difficult Feeding, *Arch. Pediat.* 32: 409, 1915.
6. Ladd, M.: Further Experience with Homogenized Olive Oil Mixtures, *Arch. Pediat.* 33: 500, 1916.
7. Utheim, K.: A Study of the Blood and its Circulation in Normal Infants and in Infants Suffering from Chronic Nutritional Disturbances, *Am. J. Dis. Child.* 20: 366, 1920.
8. Hess, J. H.: The Premature Infant, *Brennemann's Practice of Pediatrics*, vol. 1, Hagerstown, Md., 1946, W. F. Prior Company, Inc. chap. 43.
9. Adams, F. H.: A Simple Formula for Premature and Full-Term Infants, *J. PEDIAT.* 33: 23, 1948.
10. Wallace, H. M., Baumgartner, L., and Park, M.: The Average Length of Stay in the Hospital of Infants Born Prematurely, *Pediatrics* 1: 66, 1945.

PYLORIC STENOSIS IN ONE OF IDENTICAL TWINS

Roy F. GARRISON, M.D.
KANSAS CITY, KAN.

THERE has been discussion and speculation in the literature over the cause of congenital pyloric stenosis. Sheldon¹ was the first to show that when twins are involved, both will be affected if they are uniovular and only one will most likely be affected if they are binovular. This fact, along with the much higher incidence in the male, would suggest a prenatal, possibly a genetic, cause. The following report of a case in which the pyloric stenosis occurred in only one of Negro monozygous twin girls is contrary to what one would expect, and its rarity and implications are worthy of discussion. This is the first reported occurrence of pyloric stenosis in one of monozygotic twins in this country.

CASE REPORT

Twin Negro girls were born at the University of Kansas Medical Center May 1, 1947. The mother, aged 28, was gravida 3, para 2. Her blood Wassermann was 4 plus at the time of delivery, although she had received adequate antisyphilitic treatment. The cord blood Wassermann tests on the twins were negative. The gestation period was 229 days. The first stage of labor lasted one hour, fifty-seven minutes, while the second stage was eleven minutes for Twin 1 and 3 minutes for Twin 2. Twin 1 weighed 1,680 Gm. and measured 41.5 cm. Twin 2 also weighed 1,680 Gm. and was 42 cm. in length.

The weights of both babies were approximately the same until the fifteenth hospital day, when Twin 1 started gaining faster. Perhaps this could be explained on the basis that Twin 2 developed pustules about the neck and an abscess of the back on the thirteenth hospital day. By the thirtieth hospital day, Twin 1 weighed 2,365 Gm. and Twin 2, 2,280 Gm. Twin 1 began vomiting on the thirty-fourth day. By the thirty-ninth day, Twin 1 had lost to 2,300 Gm. while Twin 2 had reached 2,500 Gm. and was sent home.

The vomiting of Twin 1 became forceful and projectile. Peristaltic waves were observed. A definite, firm tumor about 1.5 cm. in diameter was palpated in the right upper quadrant. In a period of five days, 90 Gm. of weight loss were recorded. No change in the number or character of the stools was observed. On the forty-first hospital day, Twin 1 was operated upon; a pyloric tumor was found and a Rammstedt operation was done. The postoperative course was uneventful and the baby was dismissed on the eighteenth postoperative day weighing 2,675 Gm.

The proof that these girls are monozygotic twins is based on the following facts. The accompanying photograph taken when they were twenty months of age shows their identical appearance. The Department of Pathology reported that the placenta had a single chorion and two amnions. Their fingerprints were alike, but not identical. Jennings² states that the fingerprints of identical twins are as similar as those of the right and left hand in a single individual. Hoover³

From the Department of Pediatrics, University of Kansas School of Medicine.

states that in his experience the general pattern can be similar but it is recognized that there can also be differences. The weights, measurements, growth and development, blood grouping, and teething of the twins were similar, as are recorded in the Table of Comparison.

TABLE OF COMPARISON

	TWIN I		TWIN II
Birth Weight	1,680 Gm.		1,680 Gm.
Birth Height	41.5 cm.		42 cm.
Blood Group	A, Rh+		A, Rh+
First Tooth	6 mo.		6 mo.
Sat Up	4.5 mo.		5 mo.
Stood Alone	10 mo.		11 mo.
Walked	11 mo.		12 mo.
Talked	12 mo.		12 mo.
Weight at 20.5 mo.	23 pounds		22.5 pounds
Height at 20.5 mo.	31 inches		31 inches
Head circumference at 20.5 mo.	46 cm.		46 cm.
Chest circumference at 20.5 mo.	48 cm.		47 cm.
Waist circumference at 20.5 mo.	49 cm.		49 cm.
Number of teeth at 20.5 mo.	12		12



Fig. 1.—Twin 1 (left-hand side of picture) of these identical twins developed pyloric stenosis while Twin 2 did not.

DISCUSSION

There have been three reports in the literature in which pyloric stenosis has been described in only one of identical twins. One identical twin girl reported by Lasek¹ in 1925 died of influenza and was considered to have hypertrophic pyloric stenosis at autopsy. However, a pyloric tumor was not felt during life and according to Sheldon the post-mortem description of the pylorus, as given

by Laseh, was not conclusive enough to establish the diagnosis. Sheldon described identical twin boys in 1938, one of whom started vomiting from birth, was constipated, and failed to gain weight. A tumor was palpated, and at operation the diagnosis of pyloric stenosis was confirmed. Sheldon based his belief that the twins were identical on their similar appearance and the fact that "there was only one placenta without any line of fusion, and one set of membranes." Fingerprints were taken and were not facsimiles. Lewis⁵ in 1944 described a set of monozygotic twins, one of whom had obvious pyloric stenosis and was operated upon, while the other twin had no vomiting, no weight loss or stool change, but did have peristaltic waves, delayed emptying time, and a palpable tumor. He believed that both of his identical twin boys had pyloric stenosis, but in one it was asymptomatic.

The three cases cited above plus the one reported here represent the exceptions to the usual findings in identical twins. The characteristic findings have been summarized by Laubscher and Smith,⁶ who collected all the reported cases of this syndrome in twins. They found that pyloric stenosis had been reported in both twins in eleven of thirteen sets of monozygotic twins, but in only two of twenty-four sets of binovular twins. The high incidence with which pyloric stenosis has been reported in both members of a set of monozygotic twins suggests that the basis of this syndrome is primarily a genetic one. The fact that an occasional set of uniovular twins is observed in which only one of them has symptoms and signs of pyloric stenosis could be explained by the theory that the tumor is present but remains asymptomatic, as suggested by Lewis. It is generally believed that the tumor is present at or before birth. It has been stated that pyloric stenosis has been observed in stillborn infants.⁷ If the tumor is well developed at the time of birth, a latent period varying from one to several weeks elapses during which the tumor remains asymptomatic. Wallgren⁸ has shown that during this latent period roentgen studies were normal on those who subsequently developed clear-cut symptoms and findings of pyloric stenosis. His failure to demonstrate a pyloric tumor by x-ray does not preclude the presence of such a tumor during this latent period. If the tumor is present at birth and remains asymptomatic for a variable period in those who subsequently develop the definite clinical picture, it would seem to be within the realm of possibility that the tumor might be present at birth in some infants and never produce symptoms. It is suggested that Twin 2 in the present report belongs to the latter group.

REFERENCES

1. Sheldon, W., M.D.: Hypertrophic Pyloric Stenosis in One of Uniovular Twins, *Lancet* 1: 1048, 1938.
2. Jennings, H. S., Ph.D.: *Brenneman's Practice of Pediatrics*. Vol. I, Hagerstown, 1948, W. F. Prior Co., pp. 14-18.
3. Hoover, J. Edgar: Personal Communication, Dec. 3, 1948.
4. Laseh, W.: Konstitutionopathologie der "angeborenen Pylorusstenose," *Münchener Med. Wehnschr.* 72: 1155, 1925.
5. Lewis, T. L. K.: Pyloric Stenosis in Identical Twins, *Brit. M. J.* 1: 221, 1944.
6. Laubscher, J. H., M.D., and Smith, A. M.: Pyloric Stenosis in Twins, *Am. J. Dis. Child.* 73: 331, 1947.
7. Ladd, Ware, and Pickett: Congenital Hypertrophic Pyloric Stenosis, *J. A. M. A.* 131: 647, 1946.
8. Wallgren, A., M.D.: Preclinical Stage of Infantile Hypertrophic Pyloric Stenosis, *Am. J. Dis. Child.* 72: 371, 1946.

TETANY IN NEWBORN TWINS COINCIDENT WITH MATERNAL TOXEMIA

HERMAN LUBENSTEIN, M.D.
NEW YORK, N. Y.

THIE purpose of this paper is to describe the occurrence of tetany in newborn binovular twins born of a mother with toxemia of pregnancy.

The earliest mention of tetany in the newborn infant was made by Kehrer in 1913.¹ Interest in this condition lapsed until 1931, when Bass and Karelitz² reported three newborn infants with this condition. In two of these the mother's intake of vitamin D was apparently adequate. There soon followed similar case reports by Rothstein and others.³ Bass⁴ reviewed the subject in 1942, emphasizing the importance of adequate therapy and the early diagnosis. According to Bakwin,⁵ tetany of the newborn infant is related to the hypoparathyroidism which is physiologic during this age period.

In tetany which follows operative removal of the parathyroids, the serum calcium sinks to a low level and the serum phosphorus rises.⁶ Similarly, in tetany of the newborn infant the serum calcium is low and the serum phosphorus is generally high. Studies have shown a drop in the serum calcium and a rise in the phosphorus during the first few days of the neonatal period.⁵

It is hoped that this report may throw additional light on the etiology of tetany of the newborn infant.

CASE REPORT

E. B., a 30-year-old Puerto Rican housewife, was admitted to the Lincoln Hospital on April 13, 1946, with the diagnosis of placenta previa and toxemia of pregnancy, pre-eclampsia, following vaginal bleeding. She was a para ii, gravida iii whose last menstrual period was reported as either July 8 or August 8, 1945; so that she was either one month or two days before her expected date of confinement. There had been one full-term normal child fifteen years earlier and an abortion ten years earlier. Her prenatal diet contained a minimal intake of milk. During the preceding six weeks slight pretibial edema was observed. There had been a weight gain of 20 pounds in the previous two months. She was a dark, thin woman with edematous lower extremities, apparently comfortable although slightly apprehensive. The blood pressure was 146/100. The temperature, pulse, and respiration were normal. The hemoglobin was 72 per cent, the urine showed albumin 2 plus. The Wassermann was negative.

Twins were delivered by cesarean section under ether anesthesia. The patient was in good condition after operation except for a blood pressure of 180/94, which in a period of five days fell to 130/80. The urine was negative by the sixth postoperative day. The patient received the regular toxemia routine, sedation, penicillin, etc. She was discharged on April 22, 1946, in a satisfactory state of health.

On May 9, 1946, she was examined after the twins had developed tetany. She appeared slightly thin and pale, but was asymptomatic. X-ray of the long

From the Department of Pediatrics, Lincoln Hospital, Bronx, N. Y., Dr. H. S. Altman, Director.

bones was negative. The Kline test was negative, the serum calcium was 13.3 mg. per cent, the serum phosphorus 3.2 mg. per cent.

The binovular twin girls, A. and B., weighed 4 pounds, $7\frac{1}{2}$ ounces, and 5 pounds, 3 ounces, respectively, at birth. They received nothing by mouth for twenty-four hours; then 5 per cent lactose water for eighteen hours, and then a mixture consisting of evaporated milk one part, water two parts, plus 5 per cent sugar in adequate feedings every three hours. On April 22, 25 mg. of ascorbic acid and 10 drops of oleum percomorph were added. Both babies were eating well and gaining weight satisfactorily, when, at 13 days, they both developed muscular twitchings as had been observed a few hours earlier in B. In B. these were mostly rightsided, involving the fingers, eyes, and face. In A. the twitchings were mostly leftsided and involved the fingers, foot, and lower jaw. Gradually these twitchings increased in intensity and spread, becoming generalized in both babies so that by May 1, severe clonic seizures occurred frequently. Although the twitchings were generalized, there continued to be a greater localization on the right side in B. and on the left side in A. At this time both babies looked well. They both had moderately thick, mucoid discharge from the nose and A. had a temperature of 101° F. The extremities were slightly rigid and any external stimulus such as noise or handling increased the intensity of the twitchings. All reflexes were exaggerated.

A lumbar puncture on A. was completely negative; on B. was traumatic. The serum calcium on A. was 5.8 mg. per cent, the blood sugar was 72 mg. per cent, the total serum protein was 4.8 per cent, and the Wassermann negative. Serum calcium was not done on B. at this time. The blood sugar was 80 mg. per cent.

On the basis of the convulsions and the low serum calcium, a diagnosis of tetany was made and 5 c.c. of calcium gluconate solution was administered intravenously to each of the babies once daily for the next three days. Calcium chloride in doses of 10 grains three times daily and oleum percomorph, 10 drops twice daily, were also given. In addition, 5,000 units of penicillin were given intramuscularly at 3-hour intervals for five days. The response to the intravenous calcium was dramatic; the severe clonic, convulsive seizures ceased at once. Gradually, over a period of three days, the muscular twitchings became less marked, and by May 4 they disappeared completely. Examination was now entirely negative. On May 3, serum calcium of B. was 8.3 mg. per cent. On May 8, bloods showed:

- A.: serum calcium, 12.2 mg. per cent; phosphorus, 5.9 mg. per cent.
B.: serum calcium, 12.7 mg. per cent; phosphorus, 6.0 mg. per cent.

On May 11, calcium chloride therapy was discontinued. On May 16, since both babies weighed over $5\frac{1}{2}$ pounds and seemed well, they were discharged on oleum percomorph 10 drops daily and adequate feedings. A blood specimen, taken just before discharge showed the following values:

- A.: serum calcium, 5.6 mg. per cent; phosphorus, 7.7 mg. per cent.
B.: serum calcium, 5.6 mg. per cent; phosphorus, 7.1 mg. per cent.

Both babies were again given calcium chloride, 10 grains every four hours, and the oleum percomorph was increased to 20 drops daily. On May 20, examination of both babies was negative. They were asymptomatic and eating well. A blood on A. showed serum calcium 7.6 mg. per cent, phosphorus 6.5 mg. per cent, phosphatase of 8.1 units. On June 5, A. was found ill with bronchopneumonia. Both babies were readmitted to the Lincoln Hospital. Blood on A. showed serum calcium 11.2 mg. per cent and phosphorus 3.8 mg. per cent. A chest x-ray of A. showed a right upper lobe bronchopneumonia.

She responded well to penicillin and sulfadiazine. During this hospital stay, x-rays of long bones of both A. and B. showed slight elevation of the periosteum over both femurs. Both babies were discharged on July 1, in good health. At this time the serum calciums were A., 9.2 mg. per cent; B., 11.0 mg. per cent.

On May 3, 1948, the twins were just over 2 years old. Examination was negative except for a patent anterior fontanel 1 cm. in diameter observed in both. X-rays of skull and long bones of mother and babies were negative. The blood calciums and phosphorus were normal.

DISCUSSION

These two cases of tetany in newborn binocular twins of a toxemic mother present several interesting aspects:

1. The diagnosis which was made in the twins was "intracranial hemorrhage," which is said to be the most common cause of convulsions and death in premature infants. Peterman⁷ records that 122 out of 176 cases of convulsions in infants under one month of age were caused by cerebral hemorrhage. One wonders how many newborn infants who die from "intracranial hemorrhage" would show a hypocalcemia if the blood were examined.*

2. In these twins, tetanic manifestations began after four days of intensive vitamin D prophylaxis and were fully developed after eight days. Eight days of vitamin D in full dosage, did not modify the symptoms of tetany in the twins.

3. Before the onset of tetany, the food intake and the weight gain were above average. Benjamin, Gordon, and Marples⁸ report that the premature infant's ability to retain calcium is excellent, and is better from cow's milk than human milk. Pafrath and Massart⁹ report an increased mineralization in prematures on a high calcium diet even without added vitamin D. It appears that prematures can absorb and retain large amounts of dietary calcium. A history of low milk intake and, presumably, low calcium content in the prenatal diet was obtained. This may have had an influence on the production of the hypocalcemic state in the twins.

4. It is a striking coincidence that the tetany began at the same time in both twins, and that they both had an acute rhinitis at a time when none of the other infants in the premature nursery were ill.

5. The maternal toxemia of pregnancy merits consideration as a possible etiologic factor. A study of Kehrer's original report on tetany in the newborn infant revealed that, of the six cases described, there were two female infants, both premature, whose mothers had toxemia of pregnancy. One of the cases reported by Rothstein was born of a mother with pre-eclampsia. He mentions the occasional coincidence of neonatal tetany with maternal pre-eclampsia. King¹⁰ reported tetany in a mother complicating toxemia of pregnancy at parturition. She was relieved immediately of the tetany by intravenously administered calcium, and then delivered premature twins weighing 2,840 and 1,843 Gm., one of whom had slight muscular twitchings. The serum

*Editor's note: Hypocalcemia is a not infrequent accompaniment of cerebral injury in the newborn infant. The finding of a low blood calcium, therefore, by no means rules out the possibility of intracranial hemorrhage.

calciums of the babies at birth (taken after the mother received intravenous calcium prior to delivery) showed the following:

Baby 1: serum calcium, 7.0 mg. per cent; phosphorus, 7.1 mg. per cent.

Baby 2: serum calcium, 7.4 mg. per cent; phosphorus, 6.8 mg. per cent.

Mother (antepartum): serum calcium, 6.0 mg. per cent; phosphorus, 8.3 mg. per cent.

The babies received calcium and cod liver oil orally at birth, and thrived. One month later, the serum calcium of the babies was 9.2 mg. per cent. This report is analogous to ours in many respects.

A perusal of the records of Lincoln Hospital contributed some evidence of a correlation between toxemia of pregnancy and tetany of the newborn. During the period 1940-1948, ten cases of hypocalcemic tetany in babies under 2 weeks of age were observed. In two of these the mothers' charts were unavailable. Of the remaining eight babies, six were born of mothers with toxemia of pregnancy. Of the other two, one mother had cardiac decompensation, and the other showed slight albuminuria (at a subsequent pregnancy two years later she had a 2 plus albuminuria). In the last mentioned instance, fetal distress and torsion of the umbilical cord existed at the delivery. In these eight cases of tetany of the newborn infant, toxemia of pregnancy was present in six mothers and there was a suggestion of some kidney pathology in the other two mothers.

Eclampsia, the severest degree of toxemia of pregnancy, has been labeled a disease of theories since no one etiologic theory seems to be appropriate. One feature of similarity between eclampsia and tetany of the newborn infant is the convulsive tendency.

The occurrence of both conditions at the end of pregnancy, when the maternal organism is subjected to the greatest demand for calcium, and the predilection of eclampsia for twin pregnancies should engage our attention. Kidney decompensation is one of the classic features of eclampsia. This factor, in conjunction with the normally decreased renal function of the newborn infant, particularly the premature,¹¹ might be linked together in the production of the hypocalcemic state. According to Cantarow,¹² some degree of hypocalcemia occurs commonly in advanced renal failure. He ascribes this to hypoproteinemia or hyperphosphatemia or both.

In view of the above, it would appear justifiable to consider the possibility of an etiologic relationship between toxemia of pregnancy and tetany of the newborn infant.

SUMMARY

1. Hypocalcemic tetany in binovular twins of a mother with toxemia of pregnancy is reported.

2. Evidence is presented, including a review of other hospital cases, for a possible etiologic relationship between maternal toxemia of pregnancy and tetany of the newborn infant.

Blood chemical determinations were done by Miss F. Woll.

REFERENCES

1. Kehrer, E.: Die Geburtshilflich-Gynäkologische Bedeutung der Tetanie, Arch. f. Gynäkologie 99: 372, 1913.
2. Bass, M. H., and Karelitz, S.: Tetany Accompanied by Hyperpyrexia and Vomiting in First Few Days of Life, J. A. M. A. 97: 1372-1375, 1931.
3. Rothstein, J. L.: Unusual Case of Low Calcium Tetany Without Convulsions in a Newborn Infant, J. A. M. A. 105: 1189, 1935.
Rothstein, J. L.: Low Calcium Tetany in the Newborn, J. PEDIAT. 5: 341, 1934.
4. Heilman, A. M., and Rothstein, J. L.: Low Calcium Tetany of the Newborn as a Problem for the Obstetrician, Am. J. Obst. & Gynec. 29: 687, 1935.
5. Bakwin, H.: Tetany of the Newborn: A Review, J. Mt. Sinai Hosp. 9: 314, 1942.
6. Gutman, A. B.: The Parathyroid Glands: Nelson Loose Leaf Medicine 3: 311-313, 1935.
7. Peterman, M. G.: Convulsions in Childhood: Twenty-Year Study of 2,500 Cases, Am. J. Dis. Child. 72: 399-410, 1946.
8. Benjamin, H. R., Gordon, H. H., and Marples, D.: Calcium and Phosphorus Requirements of Premature Infants, Am. J. Dis. Child. 65: 412-425, 1943.
9. Passfrath, H., and Massart, J.: Langfristige Untersuchungen des Mineral und Wasserstoffwechsels bei Frühgeborenen, Zeit. f. Kinderh. 54: 343, 1933.
10. King, G. A.: A Case of Tetany Complicating Pregnancy Toxemia, J. Obst. & Gynaec. Brit. Emp. 37: 70, 1936.
11. Gordon, H. H., Harrison, H. E., and McNamara, H.: Urea Clearance of Young Premature and Full Term Infants, J. Clin. Investigation 21: 499, 1942.
12. Cantarow, A., and Trumper, M.: Clinical Biochemistry, ed. 3, revised, Philadelphia and London, 1946, W. B. Saunders Company.

PSEUDOPEPTIC ULCER SYNDROMES IN CHILDREN

S. R. WARSON, M.D., STANLEY TURKEL, M.D., AND H. S. SCHIELE, JR., M.D.
ST. LOUIS, Mo.

AS ALVAREZ² pointed out, symptomatology related to disturbances in the function of the upper gastrointestinal tract may be so similar, regardless of the presence or absence of ulcerative lesions, that the term *pseudo-ulcer* is appropriate when no structural lesions are found. However, this term is, perhaps, unfortunate in that it focusses attention on the gastrointestinal tract and fails to indicate the significance of the common symptomatology. The work of Alvarez,³ Wolff,¹⁴ and others would indicate that emotional factors can disturb the function of the gastrointestinal tract and account for much of the characteristic symptomatology. There is also considerable clinical evidence that there can be a relationship between these factors and ulcer formation. On the basis of all the evidence, every patient with symptomatology referable to the upper gastrointestinal tract should be considered from a psychosomatic point of view rather than on the basis of the presence or absence of ulcerative lesions.

The foregoing has a distinct bearing on the approach to children with gastrointestinal disorders. The danger of focussing on the stomach lies not only in the difficulties of making an accurate diagnosis of peptic ulcer in children, but, even more important, in neglecting the implications of the symptomatology as evidence of emotional disturbance which can seriously impair the development of the child. In reviewing the pediatric literature, it was found that Kennedy (1933)⁹ and later Moore (1941)¹² considered emotional factors to be unimportant in ulcer patients. Franklin (1942)⁶ discussed a case in which emotional factors were thought to be playing a role. As will be illustrated by the case histories of two patients, if ulceration is found or suspected and the child treated solely on this basis, the emotional problems will be missed or intensified.

Although the diagnosis of "peptic ulcer" in children appears to be receiving increasing attention, the condition must still be considered uncommon. In a review of all reported cases, Guthrie⁷ in 1942 came to the conclusion that peptic ulcers are rare but can occur at any age. A review of 47,353 consecutive admissions to St. Louis Children's Hospital (1934 to 1947) disclosed only eight cases in which a final diagnosis of ulcer was made. Two were girls, aged 5 and 7 years, of whom one had a chronic duodenal ulcer proved by x-ray, the other an acute gastric ulcer associated with a glioblastoma multiforme. Six were boys, aged 1, 7, 10, 11, 12, and 14 years. On the one-year-old child the diagnosis was based on the occurrence of hematemesis, but x-ray findings were negative. The 7-year-old had a duodenal ulcer proved by x-ray. The 10-year-old had a gastric ulcer associated with a brain tumor. The 11-year-old had an acute gastric

From the Psychiatric Services for Children and Child Guidance Clinic, Washington University School of Medicine.

perforation associated with acute appendicitis. The 12-year-old had a chronic duodenal ulcer proved by x-ray, as did the 14-year-old boy. Only four of these cases (a girl of 5 years, and three boys aged 7, 12, and 14 years) had the type of lesion so common in adults (about one in 12,000 admissions). The difficulty of establishing the diagnosis has been repeatedly pointed out,^{4, 5, 11} and it would appear that x-ray is the best method of doing this,¹² although it, too, offers difficulties.⁵

The following two patients, admitted to St. Louis Children's Hospital with the diagnosis of peptic ulcer, illustrate the difficulties in diagnosis and the complex and complicated situations that are revealed when such cases are approached from a psychosomatic point of view.

CASE 1.—An 11-year-old white boy was admitted in October, 1948, with complaints of intermittent abdominal pain and vomiting with no constant relationship to food over a period of two years. Several months before the onset he had an appendectomy for similar complaints, with temporary relief. At the onset, an x-ray series was reported as revealing a duodenal ulcer the size of a dime, and he was placed on a diet of milk, eggs, and strained baby foods. He continued to have episodes of abdominal pain, was hospitalized twice, and had to be given intravenous fluids because of severe vomiting. A second x-ray series in May, 1948, was reported as indicating that the ulcer had healed. However, following this, the abdominal symptoms became worse and on admission to Children's Hospital he also complained of weakness, shortness of breath, easy fatigability, dizziness, and lightheadedness.

Physical examination and laboratory findings were essentially negative. There was no evidence of bleeding in vomitus or stool. A barium series revealed no evidence of pathology and there was some question of the validity of the original diagnosis on a review of the x-rays taken at that time. On psychological studies he revealed average intelligence but was not functioning at his maximum level, probably because of an emotional disturbance which was revealed on personality tests.

Personality study.—Both parents were seen in addition to the boy, the father once, the mother several times. It was obvious that the emotional atmosphere of the home contained many sources of tension. The father, on the surface, was a hard-working, ambitious, and successful man, "self-made," until it became obvious that he had received considerable help from his wife. When the going was particularly rough he developed some type of illness through which he could receive a great deal of indulgence and support. He was overtly hostile toward the patient, revealing his own feelings about responsibilities by being very critical of his son's ability to accept responsibility and be independent. There was a close parallel between his feeling toward the patient and toward a younger brother. He frankly favored the patient's sister, aged 10 years, but would at times make efforts to give attention to the patient, usually through some type of indulgence. The mother was the peacemaker and superficially stable but she, too, had many emotional difficulties which could be related to her background. She was an only child, never saw her father after the age of 3 years when her parents were divorced, felt that she had been deprived of many things, had to become independent relatively young, suppressed her resentments, and took over more than her share of responsibilities. She was closely attached to her son and overprotective toward both children. Her deep sense of responsibility extended to her mother, who apparently had done very little for her, was in and out of the patient's home, and was a very disturbing influence because of her harshness

toward the children and the later development of a psychotic disturbance. Both parents had chronic rectal difficulties which required surgery. The sister had an emergency appendectomy two weeks before the patient's operation. The mother has been under treatment for essential hypertension.

So far as could be determined, the patient was a wanted child, at least by the mother. However, she received a rectal tear during his birth which led to a long series of rectal operations. When the patient was 7 months old, the mother went to work because the father underwent an elective rectal operation and their finances were limited at that time. While working, the mother unexpectedly became pregnant again, and with the birth of the second child her rectal difficulties increased. As an infant, the patient did not gain weight on breast feeding, was changed to artificial formulas, and became a feeding problem because no formula seemed to work well. He was trained early for bowel and bladder control by his meticulous mother, and in turn became meticulous and perfectionistic. His physical development was within normal limits although he was sickly, had frequent upper respiratory infections, mastoiditis at 3 years, and a tonsillectomy and adenoidectomy at 4 years. He was treated frequently for a chronic post-nasal discharge which cleared up almost miraculously on Benadryl and a special eliminative diet just prior to the onset of his present disturbance.

The patient never revealed much evidence of aggressiveness. His outlets were restricted by high standards set by the family, and to these he passively submitted. Although, on the surface, he had "grown-up" attitudes and interests and seemed to be quite independent, he was found to be closely attached to his mother and fearful of his father, at the same time striving to reach the father's expressed ideal of rugged independence. During the summer prior to admission he went to a camp, apparently could not tolerate the separation from his home, and the vomiting became worse. However, in the hospital it was noted that he had much more in the way of symptomatology if his mother supervised his meals. In this way he revealed the typical conflicts found to be so important by Alexander¹⁵ as a background for the development of upper gastrointestinal disorders, viz., a strong need for love and dependency, and a strong need to deny this.

Because the family lived in a distant city, the treatment situation was necessarily abbreviated and aimed primarily at revealing the emotional problems to the family, who could then get help for these in their own community. No restrictions of diet were made in the hospital and the patient lost his gastrointestinal symptoms within a few days. Concomitantly, he made an excellent relationship with the consulting psychiatrist and was able to express his feelings of fear, loneliness, and anger. "Most of my stomach trouble is due to the fact that I get angry." He seemed to get some understanding of the true basis and direction of these feelings, but this was superficial. The mother used her interviews to pour out feelings about the situation at home and the guilt she felt about acting out some of her feelings in the management of her son's life. She accepted the importance of emotional factors and recognized her own need for psychiatric help. The father used his interviews to express anger at the physicians and resentment toward his son. He had little awareness of the role his personality played in the difficulties at home, but was able to accept the fact that emotional problems were present and treatment was indicated.

A follow-up three months after leaving the hospital indicated that there has been no return of symptoms and the patient made a much better school and social adjustment after his return home. However, the situation was still precarious because the mother had not followed up on the plan of treatment, and the father's attitudes had not fundamentally changed.

While it is uncertain if this boy had an ulcer, he does have the constellation of psychogenic factors which are found to be significant in adults who develop peptic ulcers.¹ It is possible that these factors do not operate as forcefully in childhood because of the greater acceptability of dependency wishes in children than our culture allows for adults. However, in this boy's case there was constant pressure to deny dependency by a feared and punitive father, along with very little real gratification from an embittered and insecure mother. As can be readily seen, the diet of strained baby food and other restrictions served to accentuate his conflicts and problems.

CASE 2.—A 10-year-old Negro boy was admitted in September, 1948, with the chief complaint of abdominal pain and vomiting of ten days' duration. He had five similar episodes over a period of two years, lasting seven to ten days, and relieved by food and a home remedy. These were not effective in this attack, a local physician was consulted, and, after an x-ray series, a diagnosis of "peptic ulcer" was made. A series of "hip shots" was started, but after the first he complained of soreness in his hip, the treatment was discontinued, and admission to the hospital sought. There was also a complaint of "cloudy urine" with indefinite relationship to the abdominal complaints.

Physical examination and laboratory findings were essentially negative. There was no evidence of bleeding in vomitus or stool. Gastric analysis revealed no free acid in the fasting specimen and 11° of free acid after histamine. A barium series was reported as indeterminate with one observer describing an area of "prepyloric gastritis." The original films were reexamined and were considered to reveal no evidence of pathology. Psychological studies revealed the patient to be of average intelligence but functioning below this level because of his emotional disturbance. Most of his problems were found to be related to a deep-seated maladjustment and he was unusually preoccupied with eliminative and anal functions.

The patient was initially put on a diet, but his complaints persisted for several days. The hospital course was uneventful except for a barium impaction which had to be removed. He was seen by the psychiatric service during his stay and was discharged to be followed in the psychiatric outpatient department, where he has been seen regularly once a week.

Personality Study.—It was found that this patient's mother had been a patient in the psychiatric clinic in 1945. At that time she complained of tremors, sweating, smothering sensations, dysphagia, and dysphonia. She discontinued treatment after a few interviews and nothing could be learned about her problems at that time. She brought the same defensive attitudes into the treatment situation of the patient, and, although she attends regularly, has contributed very little to our understanding of his problems.

According to the mother, she was born on a farm in Arkansas and had a happy childhood. She moved to St. Louis with her family at the age of 16 years and did housework until her marriage at 21 years. She had four children, the patient being the third, and the husband deserted after the birth of the last. A brother moved in and supported the family until three years ago, when he married and moved away. The maternal grandmother then moved into the home and took care of the children while the mother worked to support them. This was approximately the time that the mother came to the clinic with her anxiety symptoms. An older brother 13 years old apparently has superior abilities and receives considerable attention for these. An older sister also apparently has superior abilities and none of the siblings are considered to have adjustment problems.

Very little is known of his birth or early development. He was breast-fed until 9 months of age, and forcibly weaned. He became a feeding problem, eating irregularly and sparingly. Toilet training was supposedly uneventful and accomplished at 18 months of age. However, there is evidence of chronic constipation and the repeated use of laxatives. At 6 years he started soiling, and this occurred frequently up to the time of admission. He would complain that his stomach hurt, refuse to go to the toilet, and then have a partial bowel movement. Punishment did not affect this. He was always a restless sleeper and has been sleeping with his grandmother. He is a chronic nailbiter.

In treatment sessions it was difficult to get this patient to verbalize his problems. He expressed considerable resentment toward his mother and siblings, feels that he has been deprived, making excessive demands, and becomes enraged when these are not met. He appears to be closest to his grandmother, who seemingly is the only one who accepts him, and submits to her discipline and punishment without evidence of overt hostility. His relationship to the therapist was passive and submissive until recently when he began to express aggressiveness in play activities. His soiling stopped, but he had one short recurrence of abdominal symptoms.

It is obvious that we are dealing with much different personality problems in this boy than the first. The somatic disturbances are more diffuse and involve the lower as well as the upper gastrointestinal tract. The level of personality development is much more immature, and, although some of the conflicts are similar, the problem-solving techniques are different. This boy's problems are more deeply seated and more handicapping from the point of view of personality development. Treatment is handicapped by the attitudes and problems of the mother, but this is to be expected because the boy's problems are undoubtedly closely related to hers.

The course of children with gastrointestinal disturbances has not been sufficiently well followed to predict what kind of problems may develop if the condition is not adequately treated. Alvarez² found that few of his "pseudo-ulcer" patients went on to develop ulcers. Also, in a survey of adult peptic ulcer patients, Klein¹⁰ found that their histories do not indicate an unusually high incidence of gastrointestinal difficulties in children. (Such retrospective studies are not too reliable because of unconscious needs for denial of these disturbances and what they mean in the psychic life of the individual.) However, as an indicator of emotional disturbance the presence of symptomatology associated with gastrointestinal dysfunction merits considerable attention, since it may reveal severe personality disorders which can seriously impair the future development of the child.

SUMMARY AND CONCLUSIONS

Similar symptomatology related to upper gastrointestinal disorders may be present with or without associated ulceration. In either instance, emotional factors may be contributing to a greater or less degree and a psychosomatic approach is necessary.

In children, ulceration is uncommon and difficult to diagnose. Treatment should be based, not on the presence or absence of ulceration, but on the total situation in which the gastrointestinal symptoms can be considered as an indicator of emotional problems.

REFERENCES

1. Alexander, Franz: The Influence of Psychologic Factors Upon Gastrointestinal Disturbances: A Symposium, Psychoanalytic Quart. 3: 501, 1934.
2. Alvarez, W. C.: Nervousness, Indigestion, and Pain, New York, 1943, Paul B. Hoeber, Inc.
3. Alvarez, W. C.: Light From the Laboratory and the Clinic on the Causes of Peptic Ulcer, Am. J. Surg. 18: 207, 1932.
4. Block, L., and Bronstein, I. P.: Chronic Peptic Ulcer in Children, J. A. M. A. 98: 2184, 1932.
5. Burdick, W. F.: Peptic Ulcer in Children, J. PEDIAT. 17: 654, 1940.
6. Franklin, A. W.: Two Cases of Duodenal Ulceration in Children, Arch. Dis. Child. 17: 95, 1942.
7. Guthrie, K.: Peptic Ulcer in Infancy and Childhood With a Review of the Literature, Arch. Dis. Child. 17: S2, 1942.
8. Jankelson, I. R.: Peptic Ulcers in Children, Am. J. Dis. Child. 44: 162, 1932.
9. Kennedy, R. L. J.: Peptic Ulcer in Children, J. PEDIAT. 2: 641, 1933.
10. Klein, Henriette: A Personality Study of One Hundred Unselected Cases Attending a Gastro-intestinal Clinic, Am. J. Psychiat. 104: 433, 1948.
11. Kraemer, M.: Chronic Ulcer in a Six-Year-old Child, Am. J. Digest. Dis. 9: 338, 1942.
12. Moore, O. M.: Peptic Ulcer in Children, Canad. M. A. J. 44: 462, 1941.
13. Newman, A.: Peptic Ulcer in Childhood, Am. J. Dis. Child. 64: 619, 1942.
14. Wolff, Harold, and Wolf, Stewart: Human Gastric Function, London, 1943, Oxford University Press.

CONGENITAL INDIFFERENCE TO PAIN

DAVID I. ARBUSE, M.D., MORTON B. CANTOR, M.D., AND PAUL A. BARENBERG, M.D.
NEW YORK, N. Y.

UNIVERSAL indifference to pain is apparently of congenital origin. Usually during the second or third year the parents notice that the child does not complain, cry, or show any sign of pain when injured, and does not react to blows, falls, cuts, bruises, burns, and even fractures of bones. In spite of this failure to react to pain, the child always identifies correctly any stimulus applied.

Ford and Wilkins¹ in 1938 reported three cases of unusual insensitivity to pain in children. Dearborn² mentioned a 54-year-old man who reported that he had never experienced pain at any time during his life except for dull headaches. He had been a professional entertainer on the vaudeville stage and invited spectators to push pins into his body. He had been insensitive to injuries as long as he could remember. He could not recall ever having had any abdominal or visceral pain of any type. The neurological examination was negative. Critchley³ mentioned a young man who did not feel pain such as is associated with the lancing of a whitlow. He recognized the pain of a pin-prick, but said "it is nothing very much." He had never been sensitive to pain.

Kunkle and Chapman⁴ described a 25-year-old white male, a corporal in the United States Army Air Force, who had an almost complete insensitivity to pain and attacks of unconsciousness beginning in childhood. The only other sensory defect was a moderate impairment of perception of heat and cold. The threshold for both superficial pain and deep somatic and visceral pain was greatly elevated. Schilder and Stengel⁵ described several patients in whom universal insensitivity to pain was associated with unilateral lesions in the cortex of the left cerebral hemisphere, chiefly in the region of the supramarginal gyrus. Three post-mortem examinations were made. These authors suggested the term "pain asymbolia."

CASE REPORT

O. M., a 7½-year-old white girl, was admitted to the pediatric service of the Morrisania City Hospital on Nov. 3, 1948, for observation. The mother stated that despite an eighteen-month stay in the first grade, the child did not talk to the teacher and would not or could not learn to read or write or to play with the other children. The child urinated and defecated in bed.

Insensitivity to pain was first noted at about 4 years of age. The mother observed that the patient did not cry or complain when she cut, bruised, burned herself, or was spanked. At the age of 6 years the child was admitted to this hospital because of second-degree burns of her right foot, buttocks, and left knee. Further investigation revealed that while the child was left in the bath tub she had turned on the hot water. She sat in the scalding water for thirty minutes without crying or calling for her mother.

The patient was one of twins and was prematurely born at the Morrisania City Hospital on June 15, 1941. She weighed 3 pounds, 5 ounces. They were the first born children in the family. The delivery was normal and spontaneous following eighteen and one-third hours of labor. The only abnormality noted at birth was a pilonidal sinus. The child was noted to have a "lusty cry" at birth and the Moro reflex was present. She sat up at one year and did not walk until 2½ years. During the first eighteen months of life, this child had been admitted to this hospital five times for various ailments, including gastroenteritis, excoriated buttocks, lobar pneumonia, upper respiratory infection, bilateral, acute, purulent, otitis media, and conjunctivitis. During her hospital residences there were repeated notations that the child was emaciated with macerated buttocks from "negligence and improper diaper care." This condition improved rapidly during each successive hospitalization. At the ages of 3 and 4 years, respectively, she had measles and chicken pox.

The family history disclosed that there were three siblings alive and well. The patient's twin had died at 6 months of age of pneumonia. One grandparent had died of tuberculosis and another was hospitalized for the same illness. An aunt was in an institution because of a mental illness. Specific inquiry did not reveal any peculiarities of behavior or known insensitivity to pain in any other member of the family.

The mother stated that while none of her children had been especially planned, she loved them all equally. However, the patient was punished more frequently as a consequence of her enuresis and her poor school work. The child has told her mother that she "would rather be hit" than be presented with "a pencil for writing and coloring." The mother ascribed her child's poor performance in school to "stubbornness." In the street, if she was hit, the patient would not strike other children nor would she cry. At home she was unduly aggressive toward the other children. She had never overtly expressed any resentment against either parent. The mother appeared to be a dull normal individual who married at the age of 16 years. She did not object to having the child sent to a convalescent home for an indefinite period. The father had been unemployed for some time and apparently made no sincere effort to obtain a job. He did not visit the patient at any time during her six-week stay in the hospital.

The child was thin (weight 33 pounds) and undersized (height 42 inches) with coarse hair, alopecia, cracked nails, hypoplastic teeth, many small, excoriated skin lesions from repeated scratching, and several keloid formations. A systolic murmur was heard at the base of the heart.

She was right-handed. The deep tendon and cutaneous reflexes, cranial nerves, and gait were normal. She manifested no objective response to pin-prick, pinching of the skin or muscles (even down to the bone), squeezing of the tendo achillis and ulnar nerves, nor to firm pressure over the supraorbital, sternal, mastoid, and suboccipital regions. Penetration of a No. 19 needle deeply into the buttock elicited no response, but when 30 c.c. of plasma was injected (a normal routine prophylactic procedure) she seemed perturbed but did not cry. The corneal reflexes were diminished bilaterally. The ciliospinal reflex

was absent. She showed a normal response when tested with the Richter dermometer and cold pressor test. The horripilatory response was normal. When a test tube of water at 120° F. was momentarily placed in her hand, she identified it as "hot" and recognized a piece of ice placed against her skin as "cold," but she did not withdraw from either stimulus.

Laboratory studies of the peripheral blood, serology, Schick, Dick, and Mantoux tests were all within normal limits. Wassermann test of the blood and the spinal fluid were negative. The cerebrospinal fluid was under normal pressure and showed no cells, normal protein, sugar, chlorides, Mazzini, and colloidal gold readings.

In the Gesell development tests she identified correctly pictures of a "boy, baby, hat, cup, shoe, flag, house, basket, nickel." She showed a definite reticence in handling test materials at first, but when they were placed in her hands, she accurately performed the simpler tests. She could pick up a ball thrown to her with practically no fumbling and could pile ten small blocks one on top of another without having them tumble. When a block fell into her lap she immediately brought her thighs together and picked up the block. She was able to build some moderately complex block formations after a demonstration by the examiner. These tests were interpreted as approximating the pattern of a 3½-year-old child. More specific testing was rather difficult. The examination had to be interspersed with play or she would refrain from talking or responding. She consistently withdrew from further testing if a crayon and paper were presented to her. This response was never overcome satisfactorily.

During her hospital stay, she spoke spontaneously and freely to all the children on the ward and to the nurses, but at times she used "obscene" language. She was overly friendly and manifested a desire for affection. She took an interest in all the events on the ward and ate ravenously. Enuresis was noted only on two occasions. One morning, when her father was supposed to visit her, she complained of a sick feeling in her stomach, regurgitated her breakfast, and ate her lunch poorly. However, after her mother's visit that same afternoon, she ate her supper well. At the time of her discharge from the hospital, six weeks after her admission, there were no changes in the neurological findings. She was happy, her skin lesions were healed, and her general nutritional status was considerably improved.

DISCUSSION

Sensitivity to painful stimuli is present in early infancy but it is not as acute as in later life. As the infant develops, it becomes more sensitive to all painful impressions until in adult life it probably has reached the acme of sensitivity. From this period until middle age, the perceptive powers probably are stationary. Then, as age advances, they again become reduced, until in old age they are once again at a minimum.

The ability to withstand pain varies not only at different ages, but also among races and individuals of the same race. People vary widely in their sensitiveness to pain and even the same individual may react differently under

different circumstances. Behan⁶ states that those of a fair and very delicate skin are most susceptible. In them, the pain receptors, because of lack of protection which is given by a thick epidermis, are more exposed and possibly more subject to irritation. They are not only very susceptible to pain but also to cutaneous irritability of any kind.

Diminished or absent pain sensibility may be present during severe emotion such as great joy, anger, and fear. Some people are unconscious of injuries which occur in states of excitement as in fighting or in competitive sports. Insensitivity to pain may be present during arduous mental work which requires intense concentration or thought, and also in states of mental exaltation, such as is exhibited by religious zealots and during manic episodes. In some cases, by sufficient training there seems to be an ability to inhibit pain perception. Others, because of intense will power or some inherent inability to perceive pain, are comparatively insensitive. Under certain circumstances people who have no analgesia may be quite insensitive to pain or injuries which under other circumstances would give rise to intense pain. Ford and Wilkins¹ assume that there are two factors in our normal response to noxious stimuli: (1) pain as a crude sensation and (2) the reaction to pain which under normal conditions is associated with appropriate emotional elements, including fear. If the latter is minimized in any way, we may become quite indifferent to the former. Their patients were able to distinguish between the sharp and blunt end of a pin and recognized slight differences in the temperatures of test tubes. They had no analgesia or loss of sensibility; they were merely indifferent to pain, and this indifference seemed to be relative in the three cases. Not having analgesia, according to these authors, they cannot be suffering from any defect in the sensory pathways of the spinal cord or the peripheral nerves, and the indifference can scarcely be due to a mental defect, as they represent average individuals of unintelligent stock. They ruled out hysteria and their psychiatric study revealed no trends indicating sadism or masochism. In all three cases their indifference to pain was discovered before the age of 3 years. They are inclined to believe that this condition is due to a congenital dysplasia involving the neural mechanisms concerned in the perception of pain, a defect comparable with color blindness, congenital word deafness, or congenital word blindness. The precise nature of this disorder of sensation is obscure. That the defect lies in the peripheral neural apparatus or spinal cord is improbable.

Since the condition seems to be of congenital origin, the possibility of a congenital defect of the nervous system was considered. Head⁷ believed that the cerebral cortex is not essential for the appreciation of pain, for the thalamus is capable of subserving such crude sensations. Kunkle and Chapman⁸ were of the opinion that the defect was in the perception of pain and that many but not all of the phenomena of reaction to pain were thereby eliminated and that their findings supported the concept that the sensory defect is central rather than in the end organs or the spinal cord. They were of the belief that pain impulses might travel far enough centrally, perhaps to the thalamus, to initiate a blood pressure rise, and then a little further en route might meet an impasse of some

sor which could prevent the subject from recognizing the experience as painful. In brief, they inferred that the sensory defect is at the cerebral or thalamic level.

Whether or not this universal insensitivity to pain signifies an asymbolia for pain analogous to a sensory aphasia is highly conjectural. Such a hypothetical condition as pain asymbolia would be a form of agnosia. In the agnosias the difficulty lies not in the appreciation of the sensory stimuli but in the interpretation and understanding of the sensation. The mild congenital word blindness which Ford and Wilkins¹ first patient exhibited might be taken to favor the idea of a lesion in the region of the supramarginal and angular gyri. The significance of Schilder's⁵ observations is not entirely clear, for patients suffering from aphasia are not the most suitable subjects for the examination of sensibility, but if we should accept his conclusions that cortical mechanisms lying in the left hemisphere are essential for the normal reaction to pain, we might consider the possibility that deficient development of such mechanisms might result in disregard of pain.

Pain is clearly a mental phenomenon. It is usually an indication that there is some disturbance of body function. There seems to be a relationship between the degree of mentality and susceptibility to pain. The higher the development and the more vivid the imagination, the greater is the susceptibility. The phlegmatic individual is not particularly affected by pain or emotion. All his sensibilities seem dulled. Psychological factors such as suggestion and diversion of attention are of considerable importance in altering the pain threshold. The apparent insensitivity to pain in certain types of hysteria, in subjects in hypnotic trances, and in the extraordinary stoicism of religious martyrs is well recognized.

Hysteria, when it produces analgesia, is the result of suggestion and most frequently the product of the examination itself. The hysterical patient is likely to give incorrect answers during the examination. The analgesia is likely to appear and disappear from time to time and to be associated with other hysterical manifestations. Although types of hysteria may occur in childhood, the writers have never seen hysterical analgesia prior to 6 years of age. In the cases reported in children, as well as in our case, the lack of any regional distribution of the sensory disturbance, which is so characteristic of the hysterical clinical picture, is especially noteworthy. The lack of this regional localization would seem to deprive the symptom of any specific psychic connotation or of any value as a significant substitutive gratification. Some psychoanalysts have claimed that insensitivity to pain may be the expression of a sadomasochistic personality. Masochists apparently delight in pain, but these children do not enjoy pain or seek injuries. They are merely indifferent to pain.

In man, pain is not absolutely essential to life or to reasonably good adjustment because other sensations may be substituted to a great degree in providing the necessary warning signals for individuals whose pain sensation is absent. Apparently, the individual can use his other equipment to help him in detecting those dangerous situations that would ordinarily indicate the use of the pain

apparatus. From childhood, we have learned to estimate the intensity of sensations so that stimuli likely to arouse pain can be avoided. The intensity of the pain depends upon the stimulus, the sensitivity of the patient, the irritability of the nerves, and the extent and number of the nerves involved. The stimuli may be of different degrees and strength, and they may be exerted continuously or intermittently. One factor of importance is the persistence with which the attention of the patient is devoted to the pain, to the exclusion of other topics.

It is necessary to differentiate between the perception of pain and the reactions to the experience. The pain threshold is defined by Hardy, Wolff, and Goodell⁸ as the amount of stimulus which will just barely produce a painful sensation under given conditions. In their analysis of the pain experience, they concluded that the pain threshold in man is relatively uniform and stable when measured in instructed subjects and is independent of age, sex, emotional state, and fatigue within the limits of the ability of the subject to maintain an unprejudiced attitude.

SUMMARY AND CONCLUSION

Insensitivity to pain is a rare anomaly and its exact nature is not defined. Examination of sensibility in children is usually difficult, and in infants only the grossest tests are possible. Indifference to pain in children is apparently of congenital origin and they are not really analgesic, hysterical, or masochistic. The diagnosis is based upon their disregard of potentially painful stimuli and upon the absence of true analgesia. Syringomyelia and defects in the spinal cord should always be considered.

Another case of congenital indifference to pain is reported. No associated neurological abnormalities were found. The mechanism of the defect is probably central. There is no indication in our case nor in the other reported cases of a lesion in any specific part of the brain.

The authors are indebted to Dr. Louis H. Barenberg, Director of Pediatrics, for permission to report this case.

REFERENCES

1. Ford, F. R., and Wilkins, L.: Congenital Universal Insensitiveness to Pain, *Bull. Johns Hopkins Hosp.* 62: 418-466, 1938.
2. Dearborn, G.: A Case of Congenital General Anesthesia, *J. Nerv. & Ment. Dis.* 75: 612, 1931.
3. Critchley, McD.: Some Aspects of Pain, *Brit. Med. J.* 2: 891, 1934.
4. Kunkle, E. C., and Chapman, W. P.: "Pain," Research Pub. Assn. for Research in Nerv. & Ment. Dis. Insensitivity to Pain in Man 23: 100-109, 1943.
5. Schilder, F., and Stengel, E.: Asymptoma for Pain, *Arch. Neurol. & Psychiat.* 25: 598, 1931.
6. Behan, R. J.: Pain, New York, 1914, D. Appleton & Co.
7. Head, H.: Studies in Neurology, New York, 1920, Oxford University Press.
8. Hardy, J. D., Wolff, H. G., and Goodell, H.: The Pain Threshold in Man, "Pain," Research Pub. Assn. for Res. in Nerv. & Ment. Dis. 23: 1-15, 1943.

AN EXPERIMENT IN SEX EDUCATION AT A BOYS' SUMMER CAMP

LAWRENCE M. SHAPIRO, M.D.
NEW YORK, N. Y.

A MOTION picture film for school children entitled "Human Growth" has been produced recently by the University of Oregon under the auspices of the S. C. Brown Trust, Division of Social Hygiene Education.

The age levels at which the film aims are the prepubertal and early pubertal periods. With a running time of about twenty minutes, the picture portrays a coeducational classroom in which the pupils view a movie explaining the beginnings of human life, the differences between male and female, and the changes that take place from infancy to adulthood. Following a classroom discussion conducted by the teacher, the audience is invited by the teacher to continue with their own discussion. Nationwide interest in this important film was aroused by a laudatory article about it published in a widely circulated picture magazine.¹ It occurred to me that a valuable experiment could be performed by showing this moving picture at Camp Northwood, a private boys' summer camp. I was interested in observing the emotional reaction of the children to a presentation of this "delicate" subject, and the extent of their understanding as evidenced by the type of questions asked after the showing of the picture. Accordingly, the film was shown on July 16, 1948, to two separate groups of approximately twenty boys each, the 11- to 12-year-olds, and the 13- to 15-year-olds. This arbitrary division was made because I felt that the nature of the questions would differ, and I was curious to see how much they would differ.

Announcement at the supper table that an educational film on the human body was to be shown that evening was the only advance notice given. Stenographic notes and wire recordings were taken of the questions and answers in each group of boys.

To the younger group preliminary remarks were made emphasizing that camping experience in its present concept is, among other things, an educational adventure in an environment close to nature. Brief mention of fundamental biologic principles presumably learned in school was followed by a short description of the format of the film. The boys were encouraged to ask questions after the completion of the movie and announcement was made that at that time all adults were to leave the auditorium.

To the older group, a simple, matter-of-fact description of the format of the film was given. It was suggested that the picture and the ensuing discussion period might augment the boys' knowledge of the subject.

The following questions were asked by each group:

THE YOUNGER GROUP

Do the sperm cells and the egg cells combine the same in all animals?
When the tube that connects the baby is cut, wouldn't it hurt the mother?

Does the uterus ever reach its original size?

The picture showed that at about the age of 22 men grow whiskers. How come a dog, when he is about one year old, and even when he is born, has a lot of hair?

What determines the sex of the child?

In the picture, you notice the sperm breaking the egg. Will you explain that?

What causes twins to be born?

My father has black hair, and my mother has blonde hair, and I have blonde hair. How is that?

What are inherited characteristics?

What causes the change of voice?

How come there are the Siamese twins, where two babies are joined together?

What will happen if a son is born and he has one color hair, and then the mother's hair turns gray? What color hair will the next son have?

Why is it that some females cannot have children?

Is it possible to stop the blood from coming out of the vagina? [referring to menstruation].

Is there anything in the male which may be compared to menstruation in the female?

Why is a baby always born? Couldn't it be a fish or something?

What are blue babies?

Why aren't any people born with blue or green hair?

What is hemophilia?

What is a cesarean operation?

Why don't all babies weigh the same?

Where does a baby come out?

How does the male cell enter into the female?

How many cesarean operations can a woman have?

What would happen if the baby is coming out of the mother and the mother gets a disease or something?

When the baby comes through the belly button, it's very small. How can it get out?

Why does the baby come out head first? Is it too heavy?

How does a horse get a baby?

Why is it that children in a family look alike, but not exactly alike?

In breeding, where the farmer helps the male horse and the female horse, suppose the male horse doesn't want to mate?

Why is it that they won't take milk from a cow until it gives birth?

Why are some babies born without part of the body, like missing a foot?

Do doctors take x-rays before the baby is born to see how it is?

If the mother is blind, can the baby be blind?

THE OLDER GROUP

Can you tell before birth if there are going to be twins?

Why, when you are born, do you look like your parents?

What causes a birthmark?

What determines the sex of the baby?

If something should happen to the mother in six months, is there any chance of the baby being saved?

In the case of stillborn children, once the child is dead inside the mother, do the hormones start to contract the uterus right after the child dies or after nine months?

What is the cause of stillbirth?

Why can't there be an abortion after three months?

Does it ever happen that the sperm doesn't reach the egg?

When do the sex glands develop?

During pregnancy, if the mother should have some kind of disease, like measles, will the baby get that disease?

What causes babies to be born one or two months late?

When a woman can't have a child, is it ever the husband's fault?

How can you overcome sterility?

When a mother and a father have different types of blood and they mate, will the baby die? I mean about the Rh factor.

When a baby is born dead, how does it get out?

Is it possible for a mother to have twins that are too big to fit, like the Siamese twins?

When the cord is cut off the baby, is it put back in the mother?

What happens to the baby's waste while it's inside the mother?

How is the sperm manufactured in the male?

Are triplets identical?

COMMENT

The results of the above experiment were gratifying. The boys of both groups accepted the presentation as an educational feature without the slightest bit of smirking or giggling. The questions were seriously asked and the answers attentively followed. As was anticipated, the questions of the older boys were more technical in nature; almost all of them were obstetrical. Interestingly enough, at the beginning these boys were less at ease than the younger group in asking questions, for they "knew all this" before. Very likely, their attitude was due to the fact that for them the acquisition of sex information was also a very personal matter. Once the questions started, however, they continued without interruption.

Frequent, seemingly casual follow-up conversations with various boys during the rest of the summer, aided by the observations of some of the counselors, failed to reveal that undue sexual excitement was aroused by the experiment. No instances were noted of changed activities among the children, nor change in relation between any boys and their campmates or counselors. Without being able to delve into the innermost thoughts of each individual boy, one received the over-all impression, nevertheless, that the children accepted the presentation as a source of specialized information, or a means of correcting misinformation, not as anything much more dramatic.

Those parents who saw the film and eavesdropped from the outside during the question and answer period were enthusiastic and grateful. Undoubtedly, to many of them this presentation to their child of a subject which they previously may have touched but gingerly represented a prop of some sort, a sharing of responsibility, as well as a source of reference for some future discussions at home. Other parents, who subsequently heard about the presentation, later expressed their approval.

It is now generally agreed that the home should be the site of primary responsibility for sex education of the child. Under optimal conditions a well-adjusted parent is intellectually and emotionally prepared to answer the early simple questions with simple, direct answers, the later more complex problems with sympathy and understanding.

Unfortunately, these optimal conditions rarely prevail. Parents of today were the sexually repressed and ill-informed children of another era, when discussion of the physiologic facts of life was taboo in most families. Consequently, most parents today are not emotionally geared to the task of handling for their children this highly personal subject matter, regardless of whether or not they have the facts straight.

I, therefore, strongly feel that, in addition, the school and the summer camp may well assume important secondary roles in the promulgation of proper sex education to children. Certainly, "Human Growth" and other similar films can be integrated in the educational program of children's camps, along with the nature study activities. Introduction to the beginnings of human life may be aided by concomitant utilization of vegetables, flowers, insects, frogs, chickens, hamsters, and rabbits. The similarities and differences between the beginnings of human life and of these lower forms will thus assume their proper significance in the inquiring mind of the growing child.

It is my belief, further, that elementary and secondary schools should use these films in like manner. Here the problem arises as to who shall instruct the students. At a camp the logical preceptor is the camp physician or nurse. But what about the schools? The University of Oregon authorities² are strongly committed to the view that the regular classroom teachers should undertake this type of instruction. They feel that "the normal teaching situation" should prevail, in order not to overdramatize a subject which is emotionally charged to begin with. At the present time, the use of the film in the Oregon schools is only just beginning, so that full evaluation of this point of view must be held in abeyance.

My personal feeling is that this subject is so special that children will not be unduly stimulated by someone other than the teacher conducting the class, provided that someone is an emotionally mature physician or nurse, possibly the school's own physician or nurse, a person who understands and sympathizes with children, a person who commands their respect. Even the Oregon authorities are aware of the fact that "there are teachers who are not sufficiently emotionally adjusted or who may not have the technical data to enable them to undertake such teaching." In the eyes of children, on the other hand, the

doctor and the nurse represent medical authority, their answers accurate and objective, their demeanor imperturbable.

I further believe that for the age levels covered in this paper, sex education, whether at camp or in school, should be presented separately to boys and to girls. Otherwise, group discussion, even under the most expert guidance, would fall far short of its greatest possibilities.

CONCLUSION

1. An experiment in sex education at a private boys' summer camp is described, utilizing the moving picture film "Human Growth."

2. A plan is suggested for sex education in summer camps and in schools.

REFERENCES

1. Life Magazine 24: page 55, May 24, 1948.
2. Personal communication from Adolph Weinzierl, M.D., Director of E. C. Brown Trust, Division of Social Hygiene Education.

Case Reports

ROCKY MOUNTAIN SPOTTED FEVER TREATED WITH CHLOROMYCETIN

REPORT OF TWO CASES

MERL J. CARSON, M.D., LEO F. GOWEN, M.D., AND FRED R. COCHRANE, M.D.
ST. LOUIS, Mo.

CHLOROMYCETIN has been demonstrated to be an effective antibiotic in experimental rickettsial infections.^{1, 2} Typhus fever³ and scrub typhus⁴ have been successfully treated with this antibiotic. It has not yet been extensively utilized in Rocky Mountain spotted fever. Pincoffs and associates⁵ reported one group of fifteen patients with this condition successfully treated with chloromyeetin. In these patients subjective improvement was noticeable on the second day of treatment. In all cases the temperature dropped to normal levels within seventy-six hours after the initial dose, with an average duration of fever of 2.2 days.

Two cases of Rocky Mountain spotted fever have been successfully treated by us with chloromyeetin.

CASE 1.—J. P., a boy, aged 3 years, was admitted to the St. Louis County Hospital on May 15, 1949, with a complaint of fever and a skin rash. Eight days before admission the parents had removed several ticks from his body. Four days later he became ill with a temperature of 101 to 103° F., and twelve hours later a rash appeared over the trunk and extremities. Several physicians were consulted during the following several days, and penicillin and sulfonamides were given without benefit. His temperature rose to 105° F., and he was admitted to the hospital.

On admission his temperature was 105.4° F., respirations 64, pulse 200. He was acutely ill. A reddish, macular rash was present over the entire body but was most marked on the extremities. Many of the lesions were purpuric. The spleen was palpable 2 cm. below the costal margin. The remainder of the examination was essentially negative. The laboratory work on admission was as follows: white blood cells, 6,100; red blood cells, 3.2 million; hemoglobin, 10.5 Gm.; differential: stab cells, 38; segmented, 33; lymphocytes 27; monocytes, 2. Agglutinations against typhoid, paratyphoid, brucella, Proteus OX19 and OXK were negative. Routine urinalysis was negative. Blood culture was sterile. Stool culture showed no nonlactose fermenting organisms.

The temperature ranged from 104.6 to 97.0° F. and back to 104.6° F. during the eighteen hours before institution of therapy. At the end of this time chloromyeetin was begun with 1.0 Gm. initial dose and 0.25 Gm. every three hours afterward. During the following day the temperature rose to 103.6° F. maximum, and on the second day of therapy the maximum temperature was 102.8° F. Sixty hours after the initial dose the temperature became normal, and he remained afebrile during the remainder of his period of hospitalization. Subjective improvement was definitely evident on the second day of therapy, and by the third day there were no subjective complaints and he felt well. The

From the Pediatric Service, St. Louis County Hospital, and the Department of Pediatrics, Washington University School of Medicine.

skin rash began to fade on the third day of therapy and had almost entirely disappeared seven days after therapy was instituted.

Five days after admission repeat agglutinations revealed a titer of 1:1,280 for both *Proteus OX19* and *OXK*. Chloromycetin was discontinued on the third day after the temperature became normal. He was discharged nine days after admission.

CASE 2.—R. P., aged 5 years, was admitted to St. Louis County Hospital on May 15, 1949, with a complaint of fever and a skin rash. Ticks had been removed from her body eight days previously. Two days following this, she became ill with fever 101 to 103° F. On the following day a reddish skin rash appeared on her trunk, extremities, and later on her face. She was treated with penicillin and sulfonamides but became steadily worse with the rash becoming more intense until her admission to the hospital.

On admission her temperature was 105.4° F., pulse 144, respirations 36. She was acutely ill with a reddish macular rash over the skin of the trunk and face but most marked over the extremities. Many of the areas were hemorrhagic. The remainder of the examination was essentially negative except for a spleen which was palpable 2 to 3 cm. below the costal margin and some injection of the right tympanic membrane. The laboratory work on admission was as follows: white blood cells, 7,100; red blood cells, 2.99 million; hemoglobin, 9 Gm.; differential: juvenile, 3; stab cells, 44; segmented, 43; lymphocytes, 10. Urinalysis was negative except for an albumin of 1 plus. Agglutinations against typhoid, paratyphoid, Brucella, *Proteus OX19* and *OXK* were negative. Blood culture was sterile. Stool culture revealed no nonlactose fermenting organisms.

During the eighteen hours before institution of therapy, the temperature ranged from 104.8 to 98° F. and back to 104.4° F. Chloromycetin was begun at the end of this period, 1.25 Gm. for the initial dose and 0.25 Gm. every three hours afterward. On the following day the temperature rose to a maximum of 103.4° F., on the second day of therapy to 102° F., and on the third day to only 100.6° F. Eighty hours after institution of therapy she became afebrile and remained so for the remainder of her period of hospitalization.

She began to improve subjectively on the second day of therapy, and the rash began to fade on the fourth day. Seven days after therapy was begun the rash had almost disappeared. Two blood transfusions and parenteral fluids were given as supportive measures.

Repeat agglutinations taken five days after admission revealed a titer of 1:1,280 for *Proteus OX19* and *OXK*.

She was discharged nine days after admission.

COMMENT

Two patients with Rocky Mountain spotted fever were treated successfully with chloromyeetin. The results were striking and agreed with the results of Pineoffs and associates.⁵ Subjective improvement was definite on the second day after institution of therapy. The temperature dropped steadily by lysis, becoming normal in one patient within sixty hours and in the second within eighty hours after the first dose was administered. The skin rash began to fade on the third and fourth days and had almost disappeared at the time of discharge, nine days after admission. No evidence of toxicity to chloromycetin was noted. The initial dose of chloromyeetin was calculated on the basis of 60 mg. per kilogram of body weight with 0.25 Gm. administered orally every three hours afterward.

REFERENCES

- Ehrlich, J., Gottlieb, D., Burkholder, P. R., Anderson, L. E., and Pridham, T. G.: *Streptomyces Venezuela, N. Sp., the Source of Chloromycetin*, *J. Bact.* 56: 467, 1948.

2. Smadel, J. E., and Jackson, E. B.: Chloromycetin, An Antibiotic With Chemotherapeutic Activity in Experimental Rickettsial and Viral Infections, *Science* 106: 418, 1947.
3. Smadel, J. E., Leon, A. P., Ley, H. L., and Varela, C.: Chloromycetin in the Treatment of Patients With Typhus Fever, *Proc. Soc. Exper. Biol. & Med.* 68: 12, 1948.
4. Smadel, J. E., Woodward, T. E., Ley, Jr., H. L., Philip, C. B., Traub, R., Lewthwaite, R., and Savoor, S. R.: Chloromycetin in the Treatment of Scrub Typhus, *Science* 108: 160, 1948.
5. Pineoffs, M. C., Guy, E. G., Lister, L. M., Woodward, T. E., and Smadel, J. E.: The Treatment of Rocky Mountain Spotted Fever With Chloromycetin, *Ann. Int. Med.* 29: 656, 1948.

EXANTHEM SUBITUM (ROSEOLA INFANTUM) COMPLICATED BY PROLONGED CONVULSIONS AND HEMIPLEGIA

DONALD D. POSSON, M.D.

ROCHESTER, N. Y.

EXANTHEM subitum has been usually considered a disease in which no complications occur. However it is common to have the disease begin with a short convolution accompanying the initial high fever. Greenthal¹ reported the incidence of convulsions in his series of cases as 6 per cent. Wallfield² reported a boy 12 years of age who developed a convolution followed by signs of encephalitis. On the third day the temperature fell to normal and the typical rash appeared. The encephalitic signs disappeared with no sequelae. Rosenblum³ in 1945 described the only case of hemiplegia resulting from exanthem subitum thus far reported. This was a 19-month-old girl who had three convulsions; one lasting for two hours. Lethargy and cervical rigidity followed the seizures and a right-sided weakness was noted. The typical rash appeared on the fourth day. The weakness of the left arm and leg cleared up completely in ten weeks.

CASE 1.—P. M. was a 15-month-old girl who had been irritable for three days, when, on Dec. 15, 1947, her temperature rose to 104.3° F. and she had a generalized convolution lasting for forty-five minutes. She was admitted to the Rochester General Hospital where, four hours later, she had another convolution lasting thirty minutes, accompanied by a fever of 106.2° F. The next day she remained stuporous, responding only when disturbed. Weakness of the right arm and leg and the right side of the face were noticed at this time. Frequent clonic movements of the right arm and the leg and the right side of the face were present for the next five days. At times generalized convulsions lasting from two to ten minutes occurred. The spinal fluid on December 18 showed 2 cells with a trace of albumin and a negative culture. The blood culture was also negative. The white blood count on admission was 4,800 but rose to 12,000 after a blood transfusion. The nonprotein nitrogen was 26 mg. per cent, blood sugar 122. The temperature dropped to normal on December 18 and a typical exanthem subitum rash developed on the following day, lasting about twenty-four hours. The stupor continued until December 26, then gradually cleared. The weakness of the face and right leg cleared almost entirely in about two months, but the right arm was still weak twelve months later, particularly the muscles of the right hand.

CASE 2.—J. B. was an 18-month-old boy who had a generalized convolution on March 18, 1948, lasting for nine hours, associated with a temperature of 105.4° F. and minimal respiratory symptoms. He was admitted to the Newark Hospital at Newark, N. Y. where he remained comatose for several days and was found to have a right hemiplegia. Treatment consisted of sodium phenobarbital, sulfadiazine, and penicillin. The temperature dropped to normal after two days. Twelve hours later the body was covered by a fine macular rash.

From the Department of Pediatrics of the University of Rochester School of Medicine and Dentistry and the Pediatric Department of the Rochester General Hospital.

He was seen by a neurosurgical consultant who diagnosed encephalitis with right hemiplegia.

Six months later, on May 3, 1948, he was admitted to the Strong Memorial Hospital because of another convulsion of ten minutes' duration associated with a fever of 104° F. and an upper respiratory infection. Normal findings were obtained from a study of the spinal fluid, the subdural fluid, x-rays of the skull, an intravenous pyelogram, an electroencephalogram, and the blood chemistry. Definite weakness of the right arm and right leg was still present.

CASE 3.—L. L. was an 18-month-old girl who had a forty-five minute convulsion and a temperature of 105° F. Chloral hydrate solution was given per rectum. Thirty minutes later she was noted to be completely disoriented although apparently conscious. The eyes were directed to the left. Definite weakness of the right arm and leg were noted.

By the following morning these signs had cleared completely and no further muscular weakness was apparent. The fever continued intermittently for three days and then remained normal. On the fourth day a typical rash was found on the trunk and face.

DISCUSSION

Nearly all physicians who are experienced in the diagnosis of exanthem subitum will agree that this is a common cause of convulsions during the second year of life. The irritability that nearly always accompanies the disease is one of its outstanding features and usually lasts for two or three days after the rash has disappeared. It is quite possible that the causative agent has a selective action on the brain tissues aside from the possible effect of the high temperature that usually accompanies the infection.

SUMMARY

Three cases of exanthem subitum are reported in which each patient developed hemiplegic weakness following prolonged convulsive seizures. It is probable that this complication of the disease may occur more frequently than is usually believed.

The author expresses his thanks to Dr. Curt Falkenheim for permission to use the third case.

REFERENCES

1. Greenthal, R. M.: Roseola Infantum, Wis. Med. J. 40: 25, 1941.
2. Wallfield, M. J.: Exanthem Subitum with Encephalitic Onset, J. PEDIAT. 5: 800, 1934.
3. Rosenbloom, J.: Roseola Infantum Complicated by Hemiplegia, Am. J. Dis. Child. 69: 234, 1945.

BACILLUS SUBTILIS SEPTICEMIA TREATED WITH PENICILLIN

MARTHA D. YOW, M.D., JOHN B. REINHART, M.D., AND LEROY J. BUTLER, M.D.
WINSTON-SALEM, N. C.

ALTHOUGH *Bacillus subtilis* is ordinarily considered nonpathogenic, a survey of the literature of the last twenty-five years revealed approximately twenty-five cases of infection due to this bacillus. In almost every case the infection followed trauma or occurred in a person chronically ill. The reported infections included panophthalmitis, iridocyclitis, pyelonephritis, pneumonia, mastoiditis, meningitis, and septicemia. There were six cases of septicemia, all of which terminated fatally. Kelemen¹ reported a fatal case of pneumonia and sepsis in the Hungarian literature in 1924. In 1925, Sweany and Pinner² reported the first case of *B. subtilis* septicemia in the American literature. This was a postmortem diagnosis in a patient with advanced tuberculosis, who at autopsy was found to have *B. subtilis* in the pulmonary lesions and in the heart's blood. Bais,³ in 1927, discussed the pathogenicity of *B. subtilis* and reported a third case of fatal septicemia due to the organism. Pellegrini⁴ and Anghelescu⁵ reported deaths due to *B. subtilis* infections in 1934 and 1937, respectively. Hull, Howie, and Bean⁶ had a patient with *B. subtilis* pyelonephritis and terminal septicemia in 1937. All of these cases occurred before the widespread clinical use of the sulfonamides and before the advent of the antibiotics. The following case is the only case of *B. subtilis* septicemia reported since sulfonamides, penicillin, and streptomycin have been available. It responded to treatment with penicillin and sulfadiazine.

CASE REPORT

W. W., a white male infant, was delivered by cesarean section at the North Carolina Baptist Hospital on May 7, 1945. The cesarean section was performed because of cephalopelvic disproportion. The infant appeared normal at birth, and weighed 9 pounds, 4 ounces. The neonatal course was uneventful and he was discharged in good condition on the twelfth day of life.

Although the child took an evaporated milk formula fairly well, he was 5 weeks old before he regained his birth weight. At 6 weeks of age he started refusing his formula. Several changes of food failed to improve his appetite and occasionally he had projectile vomiting. When he was 11 weeks old a physician elsewhere diagnosed anemia and pylorospasm. The hemoglobin at that time was 10.5 Gm. The baby was given 125 c.c. whole blood intravenously in the physician's office and was put on phenobarbital 16 mg. three times a day.

One week later, at 12 weeks of age, the child refused to eat, was fretful, became cyanotic, and was readmitted to the North Carolina Baptist Hospital.

On this admission the baby was poorly nourished and acutely ill. The skin turgor was poor, the temperature was 100.4° F., pulse 160, respirations 64, weight 9 pounds, 8 ounces. The anterior fontanel was sunken, the eyes were glazed, and the pupils were constricted. There was a Kussmaul type of respiration. The lungs and heart were normal. The abdomen was flat and soft, the liver being palpable 2 cm. below the right costal margin. The remainder of the physical examination was normal.

The clinical picture of acidosis was confirmed by a carbon-dioxide combining power of 7 volumes per cent. Other admission laboratory data were as

From the Pediatric Department of the Bowman Gray School of Medicine of Wake Forest College and the Pediatric Service of the North Carolina Baptist Hospital.

follows: In the blood, hemoglobin was 12 Gm., red blood cells 4.09 millions, hematocrit 35 volumes per cent, sedimentation rate 14 mm. per hour, white blood cells 27,350 with 71 per cent polymorphonuclears, 26 per cent lymphocytes, and 4 per cent monocytes; urine was yellow, clear, pH 6.0 specific gravity 1.015, trace of albumin, and negative for sugar, while microscopic examination (centrifuged specimen) showed 30 to 50 white blood cells per high power field, a few granular casts, no acetone or diacetic acid; stool was normal; a blood culture grew *B. subtilis* and a urine culture showed the same organism. Stool and throat cultures were not unusual.

Clinical Course.—On admission the acidosis was treated by administration of $\frac{1}{6}$ molar sodium lactate. Although the infant seemed slightly improved, after twelve hours of hospitalization the carbon-dioxide combining power was still 7 volumes per cent, the pyuria persisted and there was moderate, irregular, hyperpyrexia up to 101° F. Penicillin and sulfadiazine therapy were instituted and $\frac{1}{6}$ molar sodium lactate was given repeatedly in an attempt to correct the acidosis.

Studies suggested that the chronic acidosis was due to failure of the renal tubules to reabsorb sodium bicarbonate, as described by Dr. Alexis Hartmann.⁷ This acidosis was corrected by the daily administration of parenteral $\frac{1}{6}$ molar lactate and oral molar lactate solution.

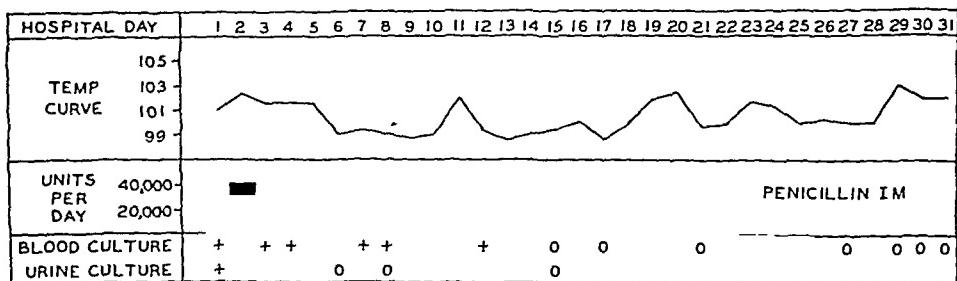


Fig. 1.

When the blood cultures were repeated on the third hospital day they again showed *B. subtilis*, fifteen to twenty colonies per cubic centimeter. It seemed probable that this organism was a contaminant, but five subsequent cultures revealed pure cultures of *B. subtilis* (Fig. 1). Urine cultures were sterile after the first hospital day. When the *B. subtilis* septicemia was fully proved, sulfadiazine was discontinued and penicillin, 40,000 units daily, was continued for twenty-one days. By the fourth hospital day the baby was greatly improved. His carbon-dioxide combining power was still fluctuating but he was alert and was eating well.

On the thirteenth day of penicillin the blood cultures became sterile and remained sterile thereafter. During the course of the septicemia and for a week after the blood cultures were sterile, the pyuria continued and the infant had a low-grade, irregular fever. After the blood stream became sterile the level of the carbon-dioxide combining power became more stable. We credited this partly to the clearing of the infection and partly to more accurate determination of the baby's daily alkali requirement after observation of his response.

At the end of thirty days the patient was afebrile and his general condition was good. His discharge weight was 11 pounds, one ounce. He was discharged on a maintenance dose of molar sodium lactate solution. The baby returned each month for regulation of his dose of molar lactate solution. Blood cultures were drawn on the first two of these monthly visits and these were sterile.

DISCUSSION

The first blood and urine cultures revealed a large, gram-positive rod. Five other blood cultures contained pure growths of the rod but repeated urine cultures were sterile. The large gram-positive rod which was consistently found had the following cultural and chemical characteristics which identified it as a strain of *B. subtilis*. It was an aerobic, spore-forming, gram-positive, motile rod. On pour plates the colonies were irregular, hemolytic, rapidly growing, and after twenty-four hours quite large. The colonies were visible within six hours after inoculation. On transplants to aerobic blood plates they were medium sized, white, wrinkled, and hemolytic. In broth the rod had a heavy growth, forming a scum on the surface. The organism alkalinized litmus milk and liquified gelatin. A 1:1,000 suspension of the organism injected intraperitoneally did not kill a mouse and the spores were not killed by boiling for ten minutes.

Most strains of *B. subtilis* are sensitive to penicillin. In fact, they are so consistently sensitive that this rod has been used in the assay of penicillin.⁸ This antibiotic would, therefore, seem ideal for treating infections due to *B. subtilis*. In vitro penicillin sensitivity tests on our organism showed it to be inhibited by a concentration of 0.1 unit per cubic centimeters. Lower concentrations were not tested. The bacillus was also tested against sulfadiazine, sulfathiazole, sulfanilamide, sulfamerazine, and streptomycin. It was not inhibited by concentrations of 12.5 mg. per cent of each of the sulfonamides but streptomycin inhibited the organism in a concentration of 8 units per cubic centimeter.

It is difficult to evaluate the role of the septicemia in this child's illness. We postulate that the baby's earlier difficulties were due to his acidbase imbalance, that the *B. subtilis* was probably introduced by contamination of the blood transfusion given one week prior to hospital admission, and that the infection precipitated the acidotic crisis. The pyuria was felt to be due to infection by *B. subtilis*. There are reports of cases of pyelonephritis proved at autopsy to be due to this organism.^{6, 9}

It is interesting to report that the boy's alkali requirement gradually diminished so that at 14 months of age the molar lactate solution could be discontinued. At that age he appeared to be a sturdy, normal boy.

SUMMARY

A case of *B. subtilis* septicemia is presented. The organism was sensitive in vitro to both penicillin and streptomycin in concentrations obtainable in vivo. Treatment with penicillin (815,000 units total dosage) was successful. Penicillin is suggested in the treatment of *B. subtilis* infections.

REFERENCES

1. Kelemen, A.: (Quoted by Sweany.²)
2. Sweany, H. C., and Pinner, M.: A Pathogenic Subtilis Bacillus From a Patient with Chronic Tuberculosis, *J. Infect. Dis.* 37: 340-343, 1925.
3. Bais, W. J.: Case of Pathogenicity of *Bacillus Subtilis*, *J. Infect. Dis.* 40: 313-315, 1927.
4. Pellegrini, F.: Contribution à l'étude de la microbiologie du "B. subtilis." Le "B. subtilis" comme cause de septicémie et de mort, *Soc. internaz. di microbiol. Boll. d. sez. ital.* 6: 492-500, 1934.
5. Anghelescu, V., and Fasic, S.: A propos des infections à *Bacillus subtilis*, *Rev. Stiint. med.* 26: 183-190, 1937.
6. Hull, E. R., Howie, J. E., and Bean, H.: Uncommon Infection of Urinary Tract with Terminal Septicemia, *Lancet* 2: 189-190, 1937.
7. Hartmann, A. F.: Clinical Studies in Acidosis and Alkalosis, *Ann. Int. Med.* 13: 940-956, 1939.
8. Schmidt, W. H., Ward, G. E., and Coghill, R. D.: Penicillin: Effect of Dissociation Phases of *Bacillus Subtilis* on Penicillin Assay, *J. Bact.* 49: 411-412, 1945.
9. Bonino, M.: "Il *Bacillus subtilis mycoides*" quale agente di pielonefrite grave conabolita funzionalità renale, *Gior. di batteriol. e immunol.* 13: 547-565, 1934.

VIRGINAL HYPERTROPHY OF THE BREAST

JAMES B. GILLESPIE, M.D., AND A. JEROME HURTER, M.D.
URBANA, ILL.

VARIOUS types of breast enlargement are encountered in pediatric practice from the newborn period through puberty and adolescence. Unilateral or bilateral enlargement frequently occurs in children of either sex and both mammary and adipose tissues may be involved. Bronstein and Cassorla¹ classified the breast enlargements in infancy and childhood in the following groups: (1) newborn type; (2) adolescent type; (3) those with associated endocrinopathies; (4) enlargements artificially induced; and (5) a miscellaneous group. In the latter group, the breast enlargements associated with cirrhosis of the liver, leucemia, testicular atrophy, carcinoma, and the so-called "mastitis gigantuan" are briefly mentioned.

Massive breast hypertrophy in adolescence has been observed occasionally and is apparently an independent entity. This condition has been termed variously as virginal, puberal, massive diffuse, or nongravid hypertrophy. Although cases have been described at a mature age or during pregnancy, the condition is usually observed at puberty, shortly before or after the menarche. Geschickter,² in a review of thirty cases of massive hypertrophy, noted that in twenty-four the onset was between 11 and 16 years of age; four others followed pregnancy, and two cases were associated with a menstrual disturbance. Bilateral involvement is most frequent, and the diffuse hypertrophy may eventually give rise to enormous pear-shaped organs.

Ordinarily after onset the enlargement goes on rapidly for a period of several months. The breasts become firm and tense, the superficial veins are dilated, and the areola are enlarged. As the weight of the breast increases it becomes pendulous, and dependent portions may be cyanotic. Pain and tenderness are transient or absent and a dragging sensation and the cosmetic deformity are the chief complaints. Mammary enlargement of considerable size may be associated with superficial ulceration of the skin.

We are reporting a case of unilateral virginal hypertrophy in a girl 12 years of age. The rarity of the condition is indicated by the paucity of reported cases and our inability to find reports of these cases in pediatric literature. This report of a case calls attention to the occasional occurrence of this unusual disorder in adolescent girls. The possibility of severe emotional disturbances in virginal hypertrophy and the radical surgery necessary for correction of the condition deserves special consideration.

CASE REPORT

R. W., a girl aged 12 years, was first seen on April 14, 1948, with the complaint of enlargement of the left breast. The birth history was normal, and the past medical history, except for the occurrence of mumps, chicken pox, rubella, and rubeola in the preschool period, was negative. She had never menstruated. The family history was essentially negative.

The patient's general health had always been excellent. For a month preceding examination she had noted that the left breast was larger than the right, and for at least two weeks discoloration of the breast had been observed.

From the Department of Pediatrics and the Department of Obstetrics and Gynecology, Carle Memorial Hospital and Carle Hospital Clinic.

Fever, local pain, or tenderness had not occurred, and breast enlargement was the sole concern of the patient and her parents.

On physical examination weight was 114 pounds, height $65\frac{1}{2}$ inches, temperature 98° F., blood pressure 116/70, and pulse 72. She was an alert, attractive, and well-looking child. Examination was essentially negative except that the left breast was enlarged, tense, slightly cyanotic, and the superficial veins were prominent in the upper quadrants. No tenderness or localized masses were noted. The areola appeared enlarged, and the nipple was retracted. There was scant axillary hair, a normal female puberal escutcheon, and the vagina and cervix appeared normal. Upon rectal examination, the uterus was found to be of normal size, and the adnexa were normal. Vaginal smears taken for estrogenic activity showed few mature vaginal epithelial cells with scant glycogen content.

Urinalysis showed a specific gravity of 1.026, acid reaction, and negative albumin, sugar, and microscopic. Blood count showed hemoglobin 14 Gm. per 91 per cent, erythrocytes 4,580,000, leucocytes 7,450, neutrophiles 64 per cent, lymphocytes 35 per cent, and eosinophiles 1 per cent. The blood Kline and Kahn tests were negative, and the sedimentation rate (Smith) showed 0.5 mm. settling in fifteen minutes and 1.5 mm. in forty-five minutes. X-ray of the chest was negative, and x-rays of the wrists showed all ossification centers present except the pisiform; the ulnar epiphysis was open.



Fig. 1.—Note the slightly pendulous breast with prominent veins in the upper quadrants.

On April 15, 1948, she was hospitalized and a diagnostic aspiration of the breast was done. No blood, pus, or tissue was obtained, and subsequently a dry dressing was applied and parenteral penicillin administered. Little change in the appearance of the breast was noted, and she was dismissed from the hospital on April 17. Later in April and in early May, three x-ray treatments were given to the breast without change in size or appearance of the breast. The breast increased gradually in size and by June 10, 1948, had become slightly pendulous (Fig. 1). By this time the mother had become most concerned about the progressive breast enlargement and presented a severe emotional problem, although the patient never seemed at all disturbed.

On June 26, 1948, a tentative diagnosis of virginal hypertrophy was made. Under Pentothal Sodium and nitrous oxide anesthesia, a biopsy of left breast tissue was obtained. Specimens were taken from the principal gland mass and

also at the junction of glandular and areolar tissue. On this date the breast appeared uniformly hypertrophic, and the enlargement was not in the form of a discrete tumor mass. Specimens from both sites were grossly firm, elastic, and of a rather homogeneous appearance.

The pathologist's report was:

"There is an abundance of ducts and the acinar structures have not appeared. In the ducts there is a thickening of lining epithelium with an increased number of cells. There is an occasional papillary excrescence with attempts to form secondary lumens. A marked increase in interstitial connective tissue is present, involving both periductal fibroblasts and those lying between the ducts. The fibroblasts appear immature and often pseudomyxomatous. Mitotic figures are present but not common, and in many areas there is deposition of immature collagen. If this specimen had been received from a more mature breast, it would be called a fetal type of fibro-adenoma. The clinical and gross pathological picture suggests virginal hypertrophy, and in this condition fibro-adenomatous growth is not uncommon. Diagnosis: Virginal hypertrophy of left breast with early fibro-adenomatous changes." (Fig. 2.)



Fig. 2.



Fig. 3.

Fig. 2.—The thickening of the lining of the ducts and the marked increase in interstitial connective tissue is prominent.

Fig. 3.—Photograph four months postoperatively.

On June 28, under Pentothal Sodium and nitrous oxide anesthesia, a simple mastectomy was done. The postoperative course was uneventful, and she was dismissed from the hospital six days following the surgical procedure.

The gross specimen (left breast) weighed 1,350 grams. Section of a surface showed a firm, rubbery, homogeneous glandular tissue of pinkish color. Microscopic findings were similar in all detail to the biopsy specimen.

She has been seen on several occasions since surgery. On the last visit, Nov. 6, 1948, she was perfectly well, normally active, and emotionally stable. The scar on the left chest was satisfactory (Fig. 3). Physical examination was essentially negative, and menstruation had not occurred at that time. In a letter from the mother, menstruation was reported to have started in December, 1948.

COMMENT

The cause of virginal hypertrophy is obscure. Schaufler³ has called attention to the fact that general hormonologic backgrounds in relation to the

breast are vague. Estrogen appears to stimulate the growth of duct epithelium, whereas progestin affects the development of the alveolae during pregnancy. A rather obscure factor, now differentiated from the anterior pituitary, and called "mammogen" supposedly stimulates the growth of the entire breast. Harris and Rosenthal⁴ considered a hormonal imbalance or continued stimulation by estrogenic substances as a possible cause of virginal hypertrophy. Certainly in this condition physiologic puerperal hyperplasia is not involved, and, therefore, the lactogenic hormone is not concerned in the process. Fisher⁵ and associates noted the possible unfavorable effects in treatment of a patient by administration of female sex hormones; during treatment the breasts increased in size. Gaines⁶ stated that the weight of evidence points to a conclusion that virginal hypertrophy is an exaggeration of normal growth seen at puberty with direct stimulus by estrogenic and possibly also the corpus luteum hormone. Abnormal sensitivity on the part of the end organ to hormonal stimuli is indicated also in those cases in which the enlargement is unilateral.

Geschickter has described the pathology of the hypertrophied breast as an exaggeration of normal adolescent development. The growth consists of an extension of ducts with marked increase in the periductal and interlobular connective tissue. Lobule formation may occur and mammary ducts show increase in size and number of their lining cells with moderate surrounding lymphocytic infiltration. The ducts are moderately dilated, but in the later stages a preponderance of sclerotic and hyalinized connective tissue compresses the ducts and leads to atrophy of many of the branches. Diffuse virginal hypertrophy may be accompanied by localized fibroadenoma, and the subsequent development of cancer and abscess formation has been reported.

In this patient, enormous breast enlargement (mastitis gargantuan) was not observed since surgical amputation was undertaken in a relatively early period. The rate of enlargement was not unusual since the period of most rapid growth is usually during the first three to four months. It would seem preferable to perform mastectomy or plastic surgery of the breast before the tremendous enlargement occurs, thus sparing these young patients the marked psychic and physical changes which may ensue. A plastic procedure was not feasible in this case since the entire breast was diffusely involved. At no time during observation of our case, either before or after surgery, was the patient disturbed, self-conscious, or apprehensive. The condition, however, became an obsession with the mother, and prior to surgery she demonstrated emotional disturbances and unusual anxiety. Such exaggerated emphasis on the enlargement by the mother over a longer period of time might have caused considerable harm. The unilateral enlargement and the occurrence prior to the menarche have been observed infrequently.

REFERENCES

1. Bronstein, I. P., and Cassorla, E.: Breast Enlargement in Pediatric Practice, *Med. Clin. North America* 30: 121, 1946.
2. Geschickter, C. E.: *Diseases of the Breast*, Philadelphia, 1943, J. B. Lippincott Company, p. 114.
3. Schaufler, G. C.: *Pediatric Gynecology*, Chicago, 1942, The Year Book Publishers, Inc., p. 171.
4. Harris, K. S., and Rosenthal, M.: Virginal Hypertrophy of the Breast, *Ariz. Med.* 2: 295, 1945.
5. Fisher, G. A., Schaufler, G. C., Gurney, C. E., and Bendshadler, G. H.: Massive Breast Hypertrophy in Adolescence, *West. J. Surg.* 51: 349, 1943.
6. Gaines, J. A.: Massive Puberty Hypertrophy of the Breasts, *Am. J. Obstet. and Gynec.* 34: 130, 1937.

THE FULMINANT FORM OF EPIDEMIC HEPATITIS IN A TWO-MONTH-OLD INFANT

FIRST LIEUTENANT ROBERT R. WILLIAMS* AND CAPTAIN BEN GABER,†
MEDICAL CORPS, ARMY OF THE UNITED STATES

TO OUR knowledge the following case is the first reported instance of the fulminant form of epidemic hepatitis occurring in an infant.

In a recent paper Lucké and Mallory¹ described the fulminant form of epidemic hepatitis. This form of the disease in adults is characterized clinically by intense severity of symptoms and death within ten days of onset. Pathologically, the distinctive findings are severe uniform autolytic necrosis of liver cells accompanied by an intensive inflammatory reaction with regenerative hyperplasia of the bile duct epithelium.

CASE REPORT

An 8-week-old male infant of Italian and German descent was admitted to the Fort Hamilton Station Hospital, N. Y., because of jaundice.

Five days before admission it was noted that his urine had become orange in color. This was accompanied by increasing yellow discoloration of the skin and paleness of the stools. No fever was noted and neither gastrointestinal nor respiratory symptoms were apparent.

The patient was the third sibling, born at term with no apparent abnormalities, weighing 5 pounds, 8 ounces. There was no family history of anemia or jaundice.

Two weeks before the onset of this illness there had been a three-day episode of diarrhea which responded to dietary measures.

Three weeks prior to the onset of jaundice, he had been cared for by a 20-year-old girl who had an upper respiratory infection.

On admission he was well-developed and weighed 8½ pounds. The skin was moderately dry and jaundiced. The conjunctivae and buccal membranes were tinged yellow. The liver edge was palpated three fingerbreadths below the right costal margin, and the spleen almost an equal distance below the left costal margin. Temperature, pulse, and respirations were normal. The remainder of the examination was not remarkable. He was fed a standard formula which he took well and retained.

On the morning of the second hospital day he vomited a few ounces of coffee-ground material. The urine was dark yellow. Other than moderate lethargy, there were no further physical findings. By afternoon the temperature had risen to 100.2° F., lethargy had increased noticeably, and the jaundice was intensified. The erythrocyte count was 3.64 million per cubic millimeter with 11.5 Gm. per cent of hemoglobin and a hematocrit of 27 per cent. The leukocyte count was 15,400 per cubic millimeter with 61 per cent lymphocytes, 34 per cent neutrophiles, 4 per cent monocytes, and 1 per cent eosinophiles. Urinalysis revealed 1 plus albumin, 1 plus sugar, a positive reaction for bile with nitric acid, a trace of acetone, and 8 to 10 pus cells per high-power field. The icteric index was 78 and the immediate direct Van den Bergh reaction was positive with 0.937 mg. per cent of bilirubin in the serum. The blood Wassermann was positive and the blood Kahn was doubtful. The blood type was O, Rh positive.

During the second night of hospitalization the infant vomited repeatedly. By early morning the temperature was 97° F. and the patient suffered a clonic convulsion of the left arm and leg lasting for eighteen minutes. Following this

*Pathology Section, First Army Area Medical Laboratory.

†Pediatric Section, Fort Hamilton Station Hospital

the respirations were rapid and labored. Coarse râles were heard throughout both lungs. The liver and spleen had decreased in size. Mild nuchal rigidity was present and the knee jerks were hyperactive. Sustained ankle clonus was elicited. Lumbar puncture showed nothing of note in dynamics, cytology, or chemistry. Oxygen and penicillin were administered, three hundred cubic centimeters of 5 per cent dextrose in distilled water, followed by 80 c.c. of whole blood were given by venoclysis. The cephalin flocculation test was reported 4 plus after twenty-four and forty-eight hours.

The clinical course deteriorated progressively. Cyanosis occurred despite oxygen. The perineum and buttocks became edematous and the patient expired on the evening of the fourth hospital day, which was the ninth day after onset of symptoms.

POST-MORTEM EXAMINATION

Complete necropsy was performed twelve hours after death. The body weight was 3,800 Gm. Development was consistent with the age of 2 months. The state of nutrition was good. The sclerae and skin were orange-green. The perineum and buttocks were moderately edematous. The pleural and peritoneal linings were orange-green, glistening, smooth, and their cavities contained no fluid. The pertinent gross changes were found in the lungs, spleen, liver and kidneys.

The lungs together weighed 85 grams. They were purple and firm, particularly in their dependent portions. The cut surfaces exuded bloody fluid.

The spleen weighed 14 grams and was softened. The sectioned surfaces were moist with blood but not diffused.

The liver weighed 99 grams, appeared to be shrunken, and was of uniform, rubbery consistency. Its external surface was smooth, patchy pink and tan. The lower edge was sharp.

The entire bile duct system appeared normal. The sectioned surface presented a nutmeg mottled pattern of pink and tan with uniform greenish tinge of minimal degree.

The kidneys were softened, their combined weight being 36 grams. They were otherwise not unusual.

MICROSCOPIC EXAMINATION*

Histopathologic findings other than those within the lungs, spleen, liver, and kidneys were not pertinent.

The lung sections showed scattered emphysema, congestion, hemorrhage, and edema. Phagocytes were numerous within the alveoli. These were unusual in that their cytoplasm contained foamy and vacuolar spaces which were identified as fat on Sudan IV stained sections. The fat droplets were generally smaller than the nucleus. No free fat or foreign material was present within the alveolar spaces.

The spleen contained diffusely enlarged malpighian follicles. Their germinal centers were widened and showed mild phagocytosis with polymorphonuclear leucocyte infiltration. The sinusoids were congested and contained moderately numerous neutrophiles, eosinophiles, and phagocytes. Erythropoietic foci were not present.

Striking changes were found within the liver (Figs. 1, 2, and 3). The parenchymal cells had undergone uniform and almost complete autolytic necrosis. A few remaining parenchymal cells could be identified singly and in groups. These were most numerous at the lobular margins and showed severe vacuolar and granular degeneration of cytoplasm with pyknosis and lysis of their nuclei. Regenerating liver cells could not be found. Many histiocytes and small amounts of cellular debris filled the inter-reticular meshes ordinarily occupied by paren-

*The histopathologic diagnosis in this case was concurred by the staff of the Army Institute of Pathology.

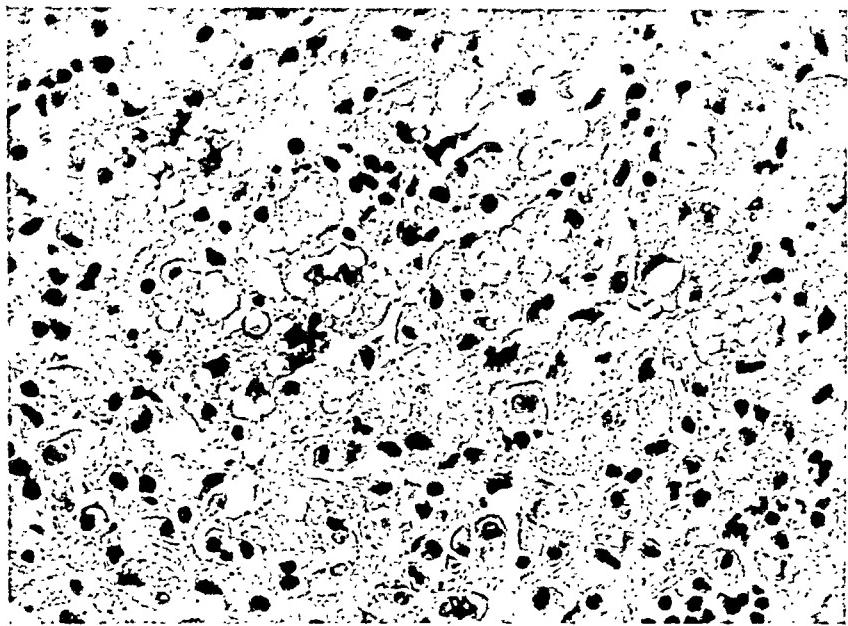


FIG. 1.—Liver, showing autolytic necrosis of hepatic cells with infiltration by histiocytes and inflammatory cells. Vacuolar degeneration of cytoplasm and karyolysis of nuclei are seen in the remaining hepatic cells.

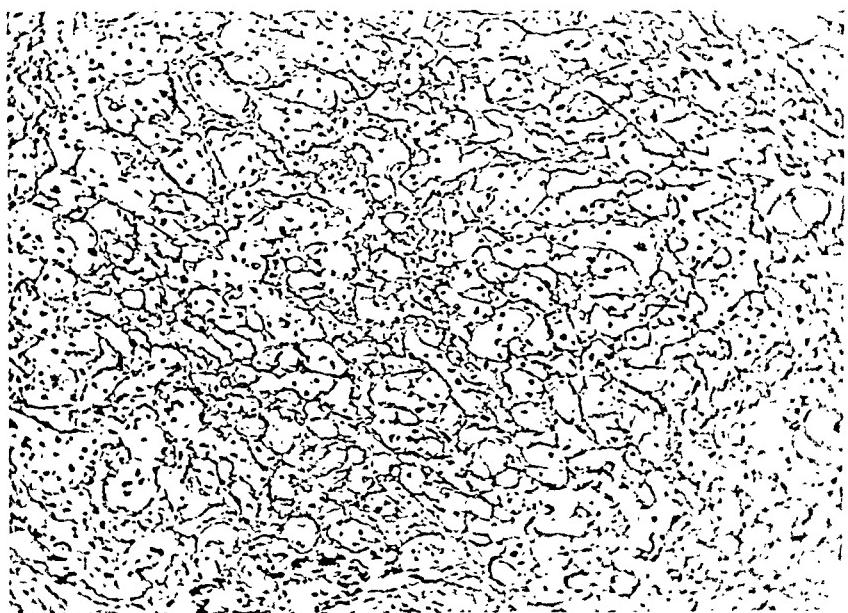


Fig. 2.—Liver, showing preservation of reticulum throughout lobule. Wilder reticulum stain.

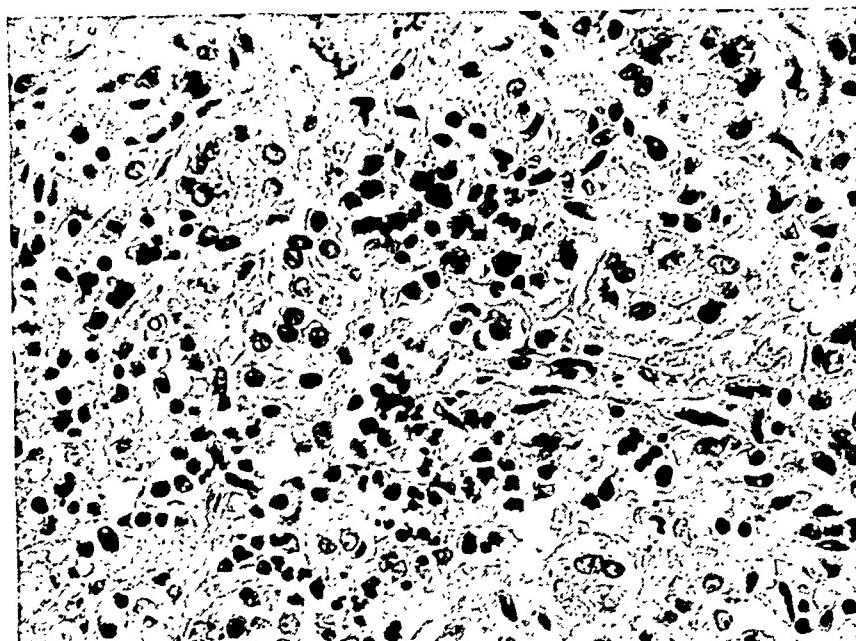


Fig. 3.—Liver, showing regenerative hyperplasia of bile ducts with polymorphous infiltration of inflammatory cells; most dense in the portal space.



Fig. 4.—Kidney, showing infiltration of tubular epithelium by sudanophilic droplets. Sudan IV stain.

chymal cells. Lymphocytes, plasma cells, neutrophiles, and eosinophiles were present throughout the liver. These inflammatory cells were most numerous in the periphery of the lobules, the perilobular stroma, and interlobular stroma. The reticulum structure of the liver was not altered in sections stained by Wilder's method (Fig. 2). Endophlebitis was not observed. Many irregular twigs of regenerating bile duct epithelium were present within the perilobular and interlobular stroma (Fig. 3).

The kidneys also presented unusual histologic findings (Fig. 4). The capsular spaces contained a small amount of albuminous precipitate, the glomeruli being otherwise unaltered. The lining cells of the proximal convoluted tubules were swollen. Within their cytoplasm were numerous foamy and vacuolar clear spaces which were small and concentrated within the basal portion of the cell. On Sudan IV stained sections they were found to contain fat. Smaller numbers of similar vacuoles were found within the epithelium of the loops of Henle, distal convoluted tubules, and collecting tubules. Sudanophilic droplets were present within the tubular lumens throughout the entire nephron. The number of fat droplets diminished gradually toward the distal portions of the tubules. Neither necrosis nor severe degenerative change was observed within the tubules.

DISCUSSION

The manner in which the infectious agent was acquired could not be determined in this case. The positive Kahn and Wassermann reactions were believed to be false, as evidence of syphilis was not found in either parent or in the infant.

Terminal neurologic findings, respiratory failure and edema of the buttocks and perineum as seen in this case were described by Lucké and Mallory in their adult cases of the fulminant form of epidemic hepatitis.¹

Epidemic hepatitis is of unusual occurrence in infants less than one year of age.^{2, 3, 4} Many cases are described in the 1- to 5-year age group.^{5, 6, 7} The course of the disease in infants and children is usually milder and of shorter duration than in adults. This point was emphasized by Horstmann and associates in a study of two epidemics.⁵

No pathologically proved cases of epidemic hepatitis terminating in death have been recorded in infants heretofore. In 1927 M. T. Morgan and H. C. Brown reported a pathologically examined case in an 11-year-old child which terminated fatally in nine days.⁸ This is the youngest proved case of the fulminant form of epidemic hepatitis which was found in a survey of the literature.

CONCLUSION

A case of the fulminant form of epidemic hepatitis has been described in an 8-week-old infant. This is believed to be the first recorded instance of this form of the disease in an infant.

REFERENCES

1. Lucké, B., and Mallory, T.: Fulminant Form of Epidemic Hepatitis, *Am. J. Path.* 22: 867-945, 1946.
2. Almering, M.: Über Hepatitis epidemica (Sog. Icterus Catarrhalis) in Sauglingsalter, *Arch. f. Kinderh.* 122: 35-48, 1941.
3. Zimanyi, I., Acholuric Catarrhal Jaundice in Infancy; Report of Case, *Arch. Pediat.* 57: 207-215, 1940.
4. Finkelstein, H., Säuglingskrankheiten, "Elsevier" Amsterdam 1938, p. 752.
5. Horstmann, D. M., Havens, W. P., Jr., and Deutsch, J.: Infectious Hepatitis in Children; a Report of Two Institutional Outbreaks and a Comparison of the Disease in Adults and Children, *J. PEDIAT.* 30: 381-87, 1947.
6. Webb, C. H., Wolfe, S. G., and Associates: Acute Hepatitis in Children; Clinical Features and Laboratory Tests, *South. Med. J.* 40: 340-9, 1947.
7. Schwartzman, J., and Maffin, A.: Catarrhal Icterus; Report of Thirty-five Sporadic Cases, *Arch. Pediat.* 57: 181-186, 1940.
8. Morgan, M. T., and Brown, H. C.: Epidemic Catarrhal Jaundice; Some Notes on Epidemiology of Disease and Account of Epidemic in Midlands, Rep. Pub. Health and M. Subj. No. 42, pp. 1-27, 1927.

Clinical Conference

WEEKLY DIAGNOSTIC CONFERENCE IN PEDIATRICS, AT THE CHARITY HOSPITAL OF LOUISIANA AT NEW ORLEANS

THIS CONFERENCE IS HELD EACH FRIDAY AT NOON, JOINTLY BY THE THREE
PEDIATRIC DIVISIONS: LOUISIANA STATE UNIVERSITY MEDICAL SCHOOL,

DR. MYRON E. WEGMAN, PROFESSOR; TULANE MEDICAL SCHOOL,

DR. RALPH V. PLATOU, PROFESSOR; AND INDEPENDENT SERVICE,

DR. ALMA SULLIVAN, IN CHARGE

DR. JOSEPH CRAVEN (Resident, Independent Division).—Are there any follow-up reports from last week?

DR. ROY A. KELLY (Resident, Louisiana State University Division).—You will recall the 9-year-old child we discussed at some length here two weeks ago, who appeared so well despite the presence of a suppurative lesion in the upper lobe of his right lung. Though the tuberculin reaction had been positive, we found no other evidence of tuberculous etiology. Lobectomy was done on the day following, and the boy has had a very smooth convalescence; our pathologists reported multiple abscesses and a mixed bacterial flora, but no evidence of tuberculosis.

DR. H. TOLMAS (Resident, Independent Division).—All the diagnostic procedures that were suggested for the 2-year-old Negro boy with apparent glycogen storage disease appeared to be confirmatory. We are now studying galactose and levulose tolerance tests with the hope that they will be helpful in guiding further management.

DR. WILLIAM NEWSOM (Resident, Tulane Division).—The very striking example of unexplained subcutaneous fat necrosis which had spread gradually to involve almost the entire back of an otherwise apparently healthy newborn infant has now cleared almost completely during the past six weeks. A biopsy confirmed our clinical impression.

Case 1. Congenital Syphilis

DR. GEORGE PRATHER (Resident, Tulane Division).—This is a white female infant who was born at home after an uneventful pregnancy; no complications were noted by the physician at the time of delivery. The infant weighed 5 pounds, 4 ounces at birth, and was breast fed for three weeks without much success. There was no appreciable weight gain, so supplementary feedings and then a number of formulas were tried. At 4 weeks the infant developed an eruption about the buttocks, considered by the mother at first to be a "diaper rash"; this gradually spread peripherally and finally involved both hands and

feet during the next week. A physician who was first consulted when the baby was 5 weeks old pronounced the child normal but for the rash which was attributed to "diapers" and "heat." No diagnostic tests were made and a salve was prescribed. There seemed to be some improvement at first, but the eruption grew worse during the next two weeks. Noisy breathing and a mucopurulent nasal discharge developed during the seventh week. There had been no apparent paralysis, and the baby had not "seemed sick." A second physician was consulted at a near-by hospital during the eighth week, and he immediately referred the patient here for therapy, with a tentative diagnosis of pemphigus and anemia.

Further history revealed that the father had been treated with penicillin for primary syphilis in May, 1947. The mother stated that she had been treated at the same institution and at the same time, but this could not be verified from the records there. One sibling, now 14 months of age, has seemed entirely normal to the mother. We examined him just last week in our clinic; he appeared well, presented no signs of syphilis, and serologic tests were negative.

At admission the clinical features of congenital syphilis in this patient were unmistakable. The infant really looked like "a little old man with a cold in the head"; she appeared malnourished, anemic, and had a generalized dusky maculopapular, vesicular, and pustular eruption which was most characteristic over the palms and soles. Where secondary infection did not interfere, the rash had a highly characteristic coppery hue with very fine and glistening superficial desquamation. There were ulcerations and excoriations about the nose, lips, and anus. There was a small mucosal "patch" over the hard palate. Scattered fine râles were heard over the right lung base; the liver and spleen were both firm, enlarged to a distance of about 4 to 5 cm. below the costal margins, and there was moderate generalized lymphadenopathy. No pseudoparalysis was noted.

A positive dark-field examination was secured immediately after admission. The hemoglobin level was 4.5 Gm. per cent, erythrocyte count 1.2 million per cubic millimeter, packed cell volume 14 per cent, leucocyte count 4,300 per cubic millimeter, with 15 per cent granulocytes, 4 per cent monocytes, and 81 per cent mature lymphocytes. Urinalysis showed nothing unusual. Both routine serologic tests were positive and the quantitative titer was 1,024 Kahn units; serologic tests from the 14-month-old sibling were negative. The infant's spinal fluid pressure was 120 mm. and the fluid was blood tinged, containing 4,000 erythrocytes, 26 lymphocytes, and 8 granulocytes per cubic millimeter; the protein level in the supernatant fluid was 31 mg. per cent and the sugar was 80 mg. per cent. Smears and cultures showed no organisms and complement fixation and colloidal gold curves yielded no abnormal results.

Therapy was started immediately—within three hours after admission—employing 100,000 units of penicillin G per kilogram of body weight divided into 100 equal doses given at three-hour intervals "around the clock." In addition, the infant has received several small transfusions, to date totalling 240 c.c., so that at present the hemoglobin level is 8.1 Gm. and the erythrocyte count is 3.8

million per cubic millimeter. Roentgenograms secured before starting therapy showed typical extensive syphilitic panosteitis and a hazy area of increased density in the base of the right lung; there were no abnormal physical signs over this area. The infant's course during therapy has been uneventful except for the fact that she developed apparent pseudoparalysis of the right arm on the twelfth day after the first dose of penicillin was given; this is still present.

DR. JOSEPH ROSENZWEIG (Resident, Tulane Division).—We often use a simple technique to obtain material for dark-field examination which is especially suitable when one does not have equipment for dark-field examination immediately available. One needs only a small piece of capillary tubing, like that used for smallpox vaccination and an ordinary sterile gauze square. Crusts or exudate are gently wiped off, then the clean surface of the lesion is irritated enough to produce a small amount of clear, serous fluid. The skin about the base of the lesion is compressed firmly between the gloved fingers for about five minutes. Tissue juice which then appears is drawn into a capillary tube, after which the ends are sealed with a flame. Such specimens can then be brought to the laboratory or held for several hours until examination can be conveniently done. The only precaution is to secure clear tissue juice; bloody specimens are difficult to examine.

At present we have three cases of congenital syphilis similar to this one on our service; among them we can demonstrate practically all the classical features of infantile syphilis. We just checked our records and found that we have treated 365 cases with penicillin since 1944; many more undoubtedly have been treated by other divisions here. Dr. Madey is visiting us from New York and I would like to know how this incidence compares with what he sees there.

DR. STEVEN MADEY (Exchange Resident, Tulane Division).—We see relatively few such cases at the Babies' Hospital because most of them are sent to Bellevue Hospital. The 1948 Public Health Reports indicated that there were 648 cases of congenital syphilis in New York City, and 13,309 cases for the entire United States. Congenital syphilis is still encountered too frequently elsewhere as well as here!

DR. RALPH V. PLATOU.—Judging by the last available national figures, syphilis accounts for four or five out of every 1,000 deaths under age one. We believe that many, if not most deaths attributed to infantile syphilis are due in reality to associated infections so common in these syphilitic babies. We believed this patient had a bacteraemia and bacterial bronchopneumonia in addition to the syphilitic lesions Dr. Prather described; hemolytic *Staphylococcus aureus* has been cultured from some of the deep skin lesions, and a number of pathogens have been recovered from the upper respiratory tract, though blood cultures remained sterile. With the treatment schedule this baby is receiving—a total of 100,000 units of crystalline penicillin G per kilogram of body weight—the prognosis is excellent if our results with many other such patients can be taken as a guide. There is probably about a 5 per cent chance of relapse during the next four to eleven months.

DR. MYRON WEGMAN.—Why was treatment started so promptly after admission?

DR. PLATOU.—The clinical diagnosis seemed obvious and an immediate dark-field examination was positive. Results of routine laboratory tests, a battery of serologic tests, and results of spinal fluid examination were returned later, though specimens were, of course, secured before therapy was started. Particularly when there is secondary infection, I think that one is justified in starting treatment with penicillin even "on suspicion" of syphilis, provided that this is preceded by collection of appropriate specimens to establish or exclude the diagnosis retrospectively. Then, even if the child turns out to be nonsyphilitic he has not necessarily been "stigmatized" by such a "panacea" as penicillin, and no harm has been done.

DR. ELLEN MACKENZIE (Fellow, Tulane Pediatrics).—Why did pseudoparalysis appear after treatment?

DR. PLATOU.—I think that is probably a matter of timing. The expected natural course of healing in osseous lesions of syphilis, judged by roentgenograms, is not altered much by treatment and is probably accelerated significantly only when therapy with penicillin is begun very early.

Case 2. Ascariasis

DR. CRAVEN.—This is a 5-year-old Negro boy, whose illness began two weeks before admission. He had had irregular fever, night sweats, a dry hacking cough, and apparently real but poorly localized pains in his chest and abdomen. His appetite had failed and he had lost approximately 4 lb. during those two weeks. The family physician had found large left epitrochlear and axillary lymph nodes, together with a mild degree of generalized lymphadenopathy, and had suspected tuberculosis.

In addition to this lymphadenopathy, physical examination revealed coarse râles bilaterally and a large, smooth liver which extended 4 cm. below the costal margin; the spleen was not enlarged. The child was quite undersized and appeared chronically ill. Roentgenograms showed a diffuse infiltration through both lung fields which was considered to be compatible with a diagnosis of tuberculosis. Repeated Mantoux tests were negative, however, as were the blood cultures and "febrile" agglutination tests, including tularemia. The blood counts were not remarkable. Ova of *Ascaris lumbricoides*, cysts of *Endamoeba histolytica*, and *Giardia lamblia* were found in the feces.

The first three nights on the ward the patient's temperature rose to 103° F. (rectally). During this period he frequently cried out because of abdominal pain, and his bowels failed to move. An enema was given on the third day and twenty adult ascaris worms were expelled. The temperature then fell to normal and he was given hexylresorcinol, 0.6 Gm., this dose being repeated five days later. He passed about 80 large worms during this seven-day period.

Following his treatment there was remarkable clinical improvement as evidenced by a weight gain of 3 lb., absence of fever, and decrease in liver size. The x-ray gradually cleared.

Although the picture is confused by the presence of *E. histolytica* in the stool, we are inclined to attribute the fever, loss of weight, and hepatomegaly to ascariasis since these symptoms disappeared following treatment with hexylresorcinol and no amebacidal drugs were given. It appears likely, therefore, that the amebiasis is incidental; of course this still will be treated. Our problem here is in deciding whether or not the ascariasis was primary or simply activated or made evident by an acute febrile illness. We frequently see patients with pneumonia or tonsillitis in whom large numbers of worms are passed during the acute febrile illness. The worms are known to migrate in the presence of fever.

Our second problem is in deciding whether to treat the patient for ascariasis while the fever is still high or to wait until the fever subsides. At one time it was considered highly dangerous to treat such patients in the face of a high fever since it was thought that treatment might stimulate the worms to migrate outside the gut or to cause intussusception. Many now feel, however, that ascariasis should be treated immediately even though the fever is high, since the high fever is known to cause migration of the ascaris on its own, and hexylresorcinol is the best agent we have for inhibiting this migration. Dr. Beaver, would you like to comment upon the optimum time for treatment?

DR. PAUL BEAVER (Tulane, Division of Parasitology).—In the past few years we have seen a gradual change in attitude regarding the optimal time for treatment. I think this change of attitude was prompted very largely by a tragic case of primary ascariasis. On admission the child was eliminating ascaris through the mouth and rectum. A large number of worms also migrated to the liver, in all probability several hours after admission, and the case ended fatally. The question arises whether or not that child might have been saved by prompt treatment. When the old drugs, santonin and oil of chenopodium, both of which are toxic, were to be used, there was reason for hesitancy. However, now with the use of hexylresorcinol, which is relatively nontoxic, early treatment should be instituted.

DR. CRAVEN.—Dr. Beaver, an interesting feature of this case was the marked hepatomegaly which we found difficult to explain.

DR. BEAVER.—With the migration of ascaris larvae from bowel to lung there are always a certain number of worms which get sidetracked, some of which may be screened out by the liver.

DR. PLATOU.—How can you say this is primary ascariasis with ascaris pneumonitis instead of ordinary bronchopneumonia in a child who has adult ascarids in the intestine?

DR. CRAVEN.—That was a difficult question to answer when the patient was admitted. However, the diagnosis was made chiefly as a result of the patient's clinical course in the hospital. The patient did not present typical physical findings of acute bronchopneumonia. The blood count did not indicate any acute ordinary bacterial infection. The x-ray appearance resembled miliary

tuberculosis more than acute bronchopneumonia. He did not receive sulfonamides or antibiotics, and his response was attributed to hexylresorcinol.

DR. PLATOU.—Has anyone ever isolated the larvae of ascaris from human lungs during life?

DR. BEAVER.—The larvae have been found in sputum, but they are very difficult to find. There are two ways in which larvae get lost in this migration from bowel back to bowel. One of them, perhaps the most common one, is by being lost in the liver. But there are also a great many lost by expectoration. If you can collect exudates in large quantities you have a fair chance in these very heavy infestations of finding at least one larva but you would need a large volume of sputum with which to work.

DR. ROSWELL JOHNSON (Tulane, Department of Pediatrics).—Dr. Beaver, do you think that eosinophilia is necessary to establish a diagnosis of pulmonary ascariasis?

DR. BEAVER.—Let us put it this way. We are always much more convinced of the diagnosis if eosinophilia occurs. This patient had just a low-grade eosinophilia, 4 per cent.

DR. RICHARD FOWLER (Resident, Louisiana State University Division).—Would you defer treatment with hexylresorcinol in the presence of diarrhea?

DR. BEAVER.—No, I would not.

DR. A. L. EXLINE (Resident, Tulane Division).—Do you use repeated courses of hexylresorcinol if the eggs persist in the stool?

DR. BEAVER.—We have seen courses of hexylresorcinol repeated every other day for as many as four times without observing any ill effects.

DR. SIDNEY CHIPMAN (Louisiana State University Department of Pediatrics).—Do you mean to imply that all larvae perish in the liver and that finding an adult ascaris in the liver indicates migration up through the bile duct?

DR. BEAVER.—Yes, the larvae either perish in the liver or pass on through to the lungs.

DR. JOHNSON.—Is there any available effective treatment for ascaris pneumonitis per se?

DR. BEAVER.—No.

DR. WEGMAN.—In view of all the publicity that has been given to amebiasis these past few years, it is interesting to see a case of ascariasis and amebiasis in which the ascariasis is emphasized and the amebiasis played down.

DR. BEAVER.—Presumably this child has had amebiasis for some time. He is one of the many in this part of the world who likewise have amebiasis, and frequently have other unrelated infections.

Case 3. Sickle Cell Disease

DR. WILLIAM STEWART (Resident, Louisiana State University Division).—This 6-year-old Negro girl was admitted with the chief complaint of pain in her legs of one week's duration. One week prior to admission the child began to complain of severe pains in her calves and thighs. The pains were so severe she would not allow anyone to touch her legs and she refused to walk. About this same time she began to have some fever, developed anorexia, and vomited occasionally. The family noted that her eyes turned slightly yellow and that her skin appeared to be paler. She was kept in bed and given Aspirin tablets with very little relief. After the symptoms had continued one week without abatement she was brought to the hospital and admitted.

The past history obtained from the patient's cousin revealed that she was in Charity Hospital at the age of 11 months for osteomyelitis of the right foot from which she recovered completely. The past history also shows that since the age of one year she has complained of periodic pains in her legs which are occasionally accompanied by fever.

The family history and social history were noncontributory. There was no history of anemia in other members of the family.

The physical examination on admission showed a thin, pale little girl, quite dyspneic and very uncomfortable. The temperature was 102° F., the pulse rate 140 per minute, and the respiratory rate 35 per minute. The sclerae were not jaundiced and the conjunctivae were very pale. The lungs were clear. The heart rate was rapid with a gallop rhythm and the heart was enlarged to the left and downward, with the PMI in the sixth interspace one centimeter outside the midclavicular line. There was a loud, blowing, systolic murmur heard best in the second left interspace but audible over the entire precordium and over the left scapula. The abdomen was soft, with the liver palpable 6 cm. below the costal margin. The spleen was not felt. There was marked tenderness and pain on motion in both lower extremities. There was no joint tenderness.

The blood count on admission showed 2.5 Gm. of hemoglobin, 1,200,000 red blood cells, 33,000 white blood cells (corrected for normoblasts), 120 normoblasts per 100 white blood cells, 10.5 per cent reticulocytes, 98 per cent sickling in twenty-four hours. The urine was negative. The one-minute direct serum bilirubin concentration was 0.6 mg. per cent and the total serum bilirubin 1.4 mg. per cent.

Shortly after admission the old chart from her previous admission at the age of 11 months was made available and revealed that at that time she had 7 Gm. hemoglobin, 2,800,000 red blood cells, 70 to 80 normoblasts per 100 white blood cells, 9.5 per cent reticulocytes, and 100 per cent sickling.

The day following admission she was given a transfusion of 250 c.c. of whole blood. After this transfusion the pulse rate slowed, she was less dyspneic, and the pains in her legs lessened but did not disappear entirely. The next day, however, her temperature again rose and she developed severe pains in the legs and abdomen. The abdomen became boardlike and very tender, and she looked much more severely ill. One hundred per cent oxygen was administered with

the presenting complaint in this child was joint pain and she has had some joint pain since admission. In both this child and a similar one in whom we tried 100 per cent oxygen when joint pain was present, no improvement was shown, but Dr. Stewart is pretty well convinced that the oxygen did not have a fair trial.

DR. PLATOU.—The diagnosis of sickle cell disease was not made when this child was 11 months old?

DR. STEWART.—Yes, the diagnosis was definitely made.

DR. PLATOU.—We have a local empiricism to the effect that dactylitis under 6 months usually is due to syphilis, after 6 months it is usually tuberculous, but at any age in a Negro it should be considered to be due to sickle cell disease until proved otherwise. I do not know how many of these we have seen but it would be interesting to add them up sometime; their number should be considerable. Reviewing the old chart some time ago, it seemed to me that the diagnosis of sickle cell disease was discarded at the age of 11 months in favor of osteomyelitis.

DR. STEWART.—No, the correct diagnosis was made then; the error came in “signing out” the chart; the correct diagnosis was not entered properly on the face sheet.

DR. WILLIAM OBRINSKY (Louisiana State University, Department of Pediatrics).—How do you account for five years of freedom from symptoms?

DR. WEGMAN.—I doubt if they were free. It is lucky that this child got away with her disease over this period of time, but it is very unfortunate that she did not have health supervision. I believe that is a serious lack in our follow-up program outside of the hospital. If she had 7 Gm. of hemoglobin then, I should imagine she has been getting along with a very low hemoglobin ever since.

DR. OBRINSKY.—But no frank crises?

DR. WEGMAN.—No.

DR. DANIEL STOWENS (Tulane, Department of Pediatrics).—Working on the basis of Dr. Tomlinson's ideas about the mechanisms for sickle cell crisis, we began treating patients in crisis with plasma rather than with whole blood. This was done somewhat empirically with the idea of “ballooning out” the whole vascular system. For a period of a year in which I saw these patients in great numbers, we were very much impressed by responses we got with plasma. We tided them over the crisis usually within twenty-four to forty-eight hours and then gave them whole blood transfusions. We never bothered to transfuse them to levels above 8 or 9 Gm. of hemoglobin, as they would not maintain higher levels very long.

DR. WEGMAN.—Dr. Kelly, when he came on rounds the next day, questioned whether we were not rather rash in transfusing this patient right away.

DR. ROY KELLY (Resident, Louisiana State University Division).—Yes. I want to know the arguments for and against transfusing patients with sickle cell

anemia in crisis. It has been said, particularly here in the Obstetrics Department, that a great deal of difficulty is seen in patients who have obstetrical complications during a crisis for which blood seems to be required. I would like to know more about this mechanism.

DR. STOWENS.—That is another point in the administration of plasma. With the peculiarities of the sickle cell, by giving plasma and oxygen we were able to increase the oxygen tension of the plasma and thereby decrease tissue anoxia.

DR. JOHNSON.—Transfusions should be avoided during these crises if possible. Oxygen is the best single therapeutic agent. Salt-poor albumin can be used to maintain blood volume. Another point to be considered here is why save such a patient from sickle cell anemia only to have her die later from serum hepatitis?

DR. STOWENS.—I think we see many more examples of sickle cell crisis than of serum hepatitis; the risk of hepatitis seems quite unimportant in this particular case.

DR. JOHNSON.—I am not so sure that this girl has been neglected. Had she been transfused many more times during the past five years she would probably have nothing more than she has now except more hemosiderosis. She is now using her iron supplies to build new blood.

Psychologic Aspects of Pediatrics

THE GIFTED CHILD

"To THEM THAT HAVE"

HARRY BAKWIN, M.D.
NEW YORK, N. Y.

THE term *gifted* is applied to individuals who are endowed with superior natural mental abilities which clearly differentiate them from the average of the same age and experience. In the larger researches, the term has been limited to children with intelligent quotients (I.Q.) of 140 and over, who normally constitute about 0.5 per cent of the population.

In 1921, Dr. Louis Terman of California and a group of associates began a long-term study of gifted children to determine what sort of adults they grow up to be. With this aim in mind over 1,500 children out of a total school population of about a quarter million were selected from the grade and high schools of California on the basis of excellence in school performance and high rating on intelligence tests. These individuals have now been observed for over twenty-five years and they form the basis of a recent publication by the California group of psychologists.¹

DESCRIPTION OF THE GROUP

Intelligence.—The original plan was to include only children with an I.Q. of 140 or above, but for various reasons sixty-two subjects with I.Q.'s between 135 and 140 were included. Most of the latter were either siblings of subjects who had already been accepted in the experimental group, or they were older adolescents whose scores seemed spuriously low because the test used at the beginning of the study (the 1916 Stanford-Binet test) does not measure high intelligence in older children with sufficient accuracy.

Since it was impossible, for financial reasons, to test all the school children, teachers were asked to name the brightest children in their classes as well as the youngest. The selected children were then given mental tests. It is of interest that the youngest child in the class qualified more often for inclusion in the gifted group than did the brightest children. Relative youth proved a better gauge for predicting intelligence than the teacher's judgment.

The mean I.Q. for the entire group was approximately 150. One girl scored 200. Six children had I.Q.'s between 190 and 194.

Sex.—There were somewhat more boys than girls (116.4 boys to 100 girls). That the preponderance of boys was not due to biased selection on the part of the teachers is indicated by the fact that of those nominated who failed to qualify for the gifted group, the proportion of males to females was the same

as that in the general population—103.7 boys to 100 girls. Terman presents evidence in favor of the view that the larger number of boys in the gifted group is due to greater variability among them,² but he is unwilling to make any positive statement.

National Origin and Race.—In comparison with the general population of the cities concerned there was a 100 per cent excess of Jewish children, a 25 per cent excess of children of native-born parentage, a probable excess of children of Scottish parentage, and a deficiency of Italian, Portuguese, Mexican, and Negro ancestry. However, nearly all the national and racial groups contributed one or more subjects to the study. "No race or nationality has any monopoly on brains." In part, at least, the representation by some groups was limited by handicaps of language, environment, and educational opportunities.

The parents of the gifted children were principally from the professional group (31.4 per cent) and the semiprofessional and business group (50 per cent). The median income for a sample of the families was more than twice that of California families in general.

Medical History and Physical Status.—No striking differences were found in the medical history and physical status. The proportion of breast-feeding was considerably in excess of that in the general population. The gifted children started to walk and talk a little earlier than others. Pubescence was also accelerated on the average. They were, if anything, less "nervous" than the generality of children. Though twice as many wore glasses as others, the incidence of defects of vision was no more frequent. In the gifted group, presumably, defective vision was more often corrected by glasses. The incidence of tonsillectomy was about twice as great as among others.

The frequency of physical defects and abnormal defects of any kind was below that found in most medical surveys of school populations. On the whole the typical gifted child was found to be a slightly better physical specimen than the generality of children as indicated by body measurements, healthy histories, and medical examinations.

Educational History.—The children liked school and most of them had skipped grades. None had been left behind. Nearly one-half had learned to read before going to school. Early indications of superior intelligence most often noted by the parents were quick understanding, insatiable curiosity, extensive information, retentive memory, large vocabulary, and unusual interest in such things as number relations, atlases, and encyclopedias.

Objective tests showed that the gifted children were 44 per cent above the average child in school achievement, indicating that the superior group, though generally advanced in school, could actually have done higher grade work. Terman estimates that more than one-half of the children with I.Q.'s of 135 and above had already mastered the curriculum to a point two full grades beyond the one in which they were enrolled and some of them as much as three or four grades beyond. The superiority of the gifted child did not relate equally to all the subjects. It was greatest in reading, language usage, arithmetical reasoning, and information in science, literature, and the arts. It was less marked

in arithmetical computation, spelling, and factual information about history and civics. But even in these subjects the gifted child surpassed the average. No correlation was found between the child's ability to achieve at school and the amount of formal schooling he had received. One child had had only two years of schooling before he entered Stanford University at 14 years of age.

The principal interests of the group under study were reading and collecting. Their play activities did not differ materially from those of the general group, although the gifted girls tended to be a little more masculine in their play life than other children. In general the play interests corresponded to those of children two to three years older.

The gifted children were found to be superior in character tests. They were less likely to be boastful or to overstate their knowledge and they were more trustworthy when under temptation to cheat. They were, as a group, more stable emotionally.

THE GIFTED GROUP AS ADULTS

As adults the gifted group showed some loss of I.Q. Terman is of the opinion that the decrease can be accounted for, in good part if not entirely, by errors in measurement and by the failure of tests in adults to measure the same mental functions as are measured by the much better standardized tests for children.

Mortality.—By 1940, when the mean age of the gifted individuals was 30 years, the death rate among male subjects was 4.14 per cent and among females 3.98 per cent, as compared with 5.02 per cent and 4.68 per cent, respectively, for comparable age groups in the general population.

Height.—The height of gifted men, as reported by themselves, averaged 5 feet, 10.65 inches, more than 2 inches above the average for unselected college men. The gifted women were .69 inches taller than the average college woman. There is, however, reason to believe that men tend to overstate their heights. Terman concludes that gifted men probably average about one-half inch taller than college men in general and gifted women show the same difference.

Physical health seemed to be at least as good as in the general population.

Mental Health.—The incidence of insanity in gifted subjects was slightly below that of the population as a whole. Alcoholism was uncommon and juvenile delinquency low. Slightly more than one per cent of the group had a history of homosexuality. About one-half of these had made reasonably normal heterosexual adjustments.

Educational Histories.—About 90 per cent of the gifted men and 80 per cent of the gifted women entered college, and 70 per cent of the men and 68 per cent of the women graduated. This percentage is approximately eight times as great as for the general population in California. In undergraduate years the social sciences were first choice as a major field by both men and women.

Of those who graduated, 68 per cent of the men and 60 per cent of the women returned for graduate study. About one-half of the men and one-third of the women received graduate degrees. A law degree was taken most fre-

quently, with the M.A., Ph.D., and M.D. following in that order. Fifty-two received the M.D. degree.

Though the average grade in college was superior, it was not always as high as might have been expected. Almost 8 per cent of the men and 2 per cent of the women flunked out. The average I.Q. of those who failed was slightly below that of the graduates. Failure was attributed to habits of idleness, unwillingness to do routine assigned tasks, excessive amount of work for self-support, or the deliberate choice to give preference to social and extracurricular activities. Occasionally physical illness and social maladjustment or immaturity were factors.

More than one-third of the men who graduated earned one-half or more of their undergraduate expenses, as compared with 16 per cent of the women. Less than 23 per cent of the men graduates earned none of their expenses.

The gifted individuals participated in extracurricular activities to a greater extent than the average students.

Occupation.—Almost one-half of the gifted men chose one of the professions as a career and about one-fourth more were in semiprofessional or higher business occupations. On the whole, they were filling positions of responsibility and leadership to a greater extent than the average college graduate. A few (6 per cent), however, were employed as minor clerical workers, policemen and firemen, and semiskilled craftsmen. One worked as a truck driver and six were in occupations requiring little skill, training, or ability. Twelve per cent were engaged in farming and other agricultural pursuits. Only 6 per cent of the group entered medicine but it is gratifying that the highest median income among the professions was earned by physicians.

Income.—On the whole the earned incomes of the members of the gifted group were higher than those of college graduates in general and considerably higher than those of unselected men and women. The men in the semiprofessional and business group had the highest incomes, the professions came next, and the clerical workers, salesmen, retail business, and skilled trade occupations ranked third. The college graduates did better, financially, than the nongraduates.

Avocational Pursuits.—A characteristic of the gifted person is an active interest in avocational pursuits. Nearly two-thirds of the group reported active interest in two or more of these and one-third reported three or more. Sports held first place among both men and women with photography second among men and music second with women. Music rated third with men, gardening with women. As for amount of interest in twelve specific fields, travel and science were first among men and travel and literature among women. Religion rated lowest with both sexes. On the whole, men who were successful in their vocations had greater interest in outside fields than the men who were least successful. In reading, literature and history were by far the most popular among both men and women. More women than men preferred fiction.

Politics.—As to political alignment, 45.2 per cent of the men and 41.6 per cent of the women said they were "Republicans" or "conservatives" and 40.0

per cent of men and 41.3 per cent of the women classified themselves as "liberal," "New Deal" or "Democrats." The number of radicals was very small. Among the professional groups author-journalists rated themselves as by far the most radical. Chemists, physicians, engineers, and lawyers were the most conservative, with teachers holding an intermediate position. The higher income groups were more conservative than the lower. There was no difference between the college graduates and nongraduates. In both sexes the tendency toward socialism was greatest among those whose emotional life was rated as unsatisfactory.

Subjects with very much interest in science or politics were more radical than others. Jewish men were slightly more radical than the non-Jewish; the Jewish women were distinctly more radical. There were fewer extreme scores, either radical or conservative, among the Jewish than the non-Jewish subjects.

Marital Status, Offspring.—Both men and women in the gifted group married as frequently and at about the same age as the California population as a whole. However, the incidence of marriage was greater and the age at the time of marriage lower than among college graduates in general. The difference was especially striking for the women. As might be expected, the gifted individuals chose spouses of comparably high intelligence. Nearly three-fourths of the husbands and over two-thirds of the wives had attended college for one or more years.

The average number of children of the gifted individuals who had been married five years or more was 1.52. The mean I.Q. of 384 offspring was 127.70. There was a low incidence of feeble-mindedness and border-zone mentality. The proportion of children with an I.Q. of 150 or over was about twenty-eight times that expected in the general population. The mortality among offspring was far below that for the general population.

The divorce rate by 1945, when the average age of the group was a little below 35 years, was 14.4 per cent for the men and 16.3 per cent for the women. It is not possible to make comparisons with the population in general or with college graduates since accurate data for these latter groups are not available. In the gifted group divorcees were less than one-half as frequent among college graduates as among nongraduates.

Subjects of I.Q. 170 or Over.—Among the living gifted group in 1940 there were forty-seven men and thirty-four women with I.Q. of 170 or more. In the general population only about three children in 10,000 may be expected to test as high as this. The high group learned to read earlier than the remainder of the gifted group and they completed grade school 8.4 months younger. They were graduated from high school and college about 9.6 months younger but the difference was not marked for the women. The high group did not differ materially from the others in physical health, nor was any difference found in "nervous symptoms" or "mental adjustment." This is of particular interest since the individuals with very high I.Q. have been considered especially prone to neurotic behavior. Social adjustment was as good as for the gifted group as a whole.

The high group did exceptionally well at college. However a good many of them did not achieve as well as might be expected. They chose, for the most part, the professions (61.6 per cent as against 45.4 per cent for the group as a whole). Of the twenty-seven men in the professions none chose medicine; nor, for that matter, did any of the very high I.Q. women. The average income did not differ materially from that of the gifted group as a whole.

THE PROBLEM OF SCHOOL ACCELERATION

Terman discusses at some length the problem as to whether children of high I.Q. should be allowed to become accelerated in school or whether they should remain in classes with children of their own chronologic age. A third alternative is to provide special classes with an enriched program for the gifted. There are such classes in many communities and it is Terman's opinion that their value has been thoroughly demonstrated. Unfortunately they are available to only a small minority of gifted children and the choice therefore rests between acceleration and nonacceleration. Terman concludes that, by and large, children of 135 I.Q. or higher should be promoted sufficiently to permit college entrance by the age of 17, or, better, 16 years. The risk of maladjustment when a young child of high I.Q. is put with older children of his same mental age is less than is commonly believed. There is, on the other hand, a very real danger that the bright child, in a class with children of his own chronologic age, will fail to develop the ambition and habits of work necessary for success in college.

FACTORS IN THE ACHIEVEMENT OF GIFTED MEN

An important part of the Terman study has been to discover what factors and circumstances are correlated with adult achievement. Although most of the individuals in his gifted group achieved positions of eminence and leadership, a sizable proportion chose lowly positions in which their intelligence level could be of little use to them or they failed to attain more than average success in their chosen professions.

In order to assess the factors which make for vocational success or failure the most successful members of the group were compared with the least successful. The selections were made by three judges working independently. Each case on which there had been disagreement was discussed and a final decision was made by majority vote. The primary criterion of success was the extent to which a subject had made use of his superior intellectual ability. If he had chosen a university career or a profession, recognition in the chosen field counted heavily and earned income received little weight unless it seemed to be a measure of success. In business or the semiprofessional pursuits, on the other hand, earnings were given more consideration. The study was limited to men since the criteria for success in women are so difficult to estimate.

To make the contrasts as sharp as possible the 150 most successful men (Group A) and the 150 least successful (Group C) were selected for study.

The A group included all men who were listed in *Who's Who* and in *American Men of Science*, a large majority of those whose university rank was above

that of instructor, and men who were outstandingly successful in the professions and in business, as well as a few who achieved most in literature, art, motion pictures, or radio.

Though the C group consisted principally of men in skilled and semiskilled trades, clerical and minor business positions and civil service jobs, it also includes a few classified as professional, semiprofessional, and managerial whose records of accomplishment were unimpressive. The average I.Q. of the A's was slightly greater than that of the C's but there was much overlapping of scores. In fact the mean of the C's was so high as to be equalled by only 15 per cent of students in superior universities.

Earned Income.—Though earned income was given relatively little weight in classifying the subjects, the average income for the A's was more than 2.5 times that of the C's.

Amount of Education.—Ninety per cent of the A's had graduated from college and 76 per cent had done one or more years of graduate work. The corresponding figures for the C's were 37.2 per cent and 14.7 per cent. Difference between the two groups in school achievement were already apparent in high school and became more marked at the college level.

Vocational Interest.—More of the members of the A group than the C group had chosen their lifework and liked their work. On the other hand, more of the C's had drifted into their jobs and almost five times as many as A's said that they would prefer some other kind of work.

Family backgrounds differed markedly for the two groups. More than three times as many A fathers as C fathers had graduated from college and there was a similar difference for the siblings. More than twice as many of the A fathers as C fathers were in the professional class. There were three times as many individuals of Jewish descent among the A's as among the C's. Childhood ratings for emotional stability, social adjustability, and various traits of personality were lower in the C's than in the A's. There was no difference in physical health.

Marriage.—The marriage rate was lower for the C's than the A's but the incidence of divorce was twice as great. The A's chose wives who were more nearly their mental equals as indicated by mental tests and amount of schooling.

Personality Ratings.—The A's rated far higher than the C's in perseverance, self-confidence, integration toward goals, and absence of inferiority feelings. The A group also outranked the C's in appearance, attractiveness, alertness, poise, attentiveness, curiosity, and originality. All in all the greatest contrast between the two groups was in the drive to achieve and in all-around social adjustment. Terman points out that contrary to the view of many to the effect that great achievement is usually associated with emotional tensions which border on the abnormal, in the gifted group success was associated with a well-balanced temperament and the absence of excessive frustration.

APPRaisal OF ACHIEVEMENT

Terman's study shows clearly that superior mentality in childhood is predictive of superior achievement in adult life. Twenty-five years after the subjects were selected solely on the basis of a high intelligence score, almost one-half of the men and more than one-half of the fully employed women are in one of the professions and another 30 per cent of the men are in the semi-professional and higher business category. During the depression, when 15 to 20 per cent of the employable males in California, where the study was carried out, were out of work, the proportion of unemployed among the gifted men was not over one per cent. Nearly 70 per cent are college graduates and 29 per cent took graduate degrees. Earned income was considerably above average.

By the end of 1945, when the average age of the subjects was close to 35 years, about ninety books or monographs and about 1,500 articles had been published by members of the group. Patents granted to members of the group number more than 100. The group includes twenty to twenty-five scientists whose achievement has already won for them a national reputation or appears likely to do so. Among the best candidates for outstanding achievements are a dozen or more of the men who have gone into medicine.

WAR RECORDS

Military Service.—Of the 760 men on whom information was secured, 42.5 per cent served in the armed forces during the war and an additional 1.2 per cent were in the Merchant Marine. Six men registered as conscientious objectors. In view of the fact that more than one-half of the gifted men were over 30 years of age when America entered the war, it is noteworthy that the proportion enrolled in the armed services exceeded that for all males in the country aged 18 to 44 years. Terman estimates that the number rejected as physically or mentally unfit was far below the average for the country as a whole.

Though about one-half of the men in the Army entered as privates, 70 per cent were commissioned officers at the time of discharge and 75 per cent of the men were commissioned officers on discharge from the Navy. With the records still incomplete, 22 per cent of the men received one or more citations.

Many more of the A's than the C's received commissions. In the A group, 82 per cent were discharged as commissioned officers in the Army and 89 per cent in the Navy. The corresponding percentages for the C group were 33 and 13.

SUMMARY

1. Terman's follow-up study of gifted children into adult life is reviewed. The study was begun in 1921 and the average age of the group in 1945 was 35 years.

2. Gifted children are, as a rule, superior to the general child population in physique and general health and the later mortality up to the age of 35 years is lower. It is not clear how much of this is to be credited to better home environment.

3. Throughout the educational period, the achievement of gifted children is superior to others, although a good many make poor or mediocre records in college.

4. The achievements of gifted children are versatile rather than one-sided, and they generally do well in all school subjects.

5. The typical gifted child is customarily held to a grade well below his ability.

6. Gifted children who have been promoted rapidly are, as a group, superior to gifted nonaccelerates in health and general adjustment. They do better school work and are more successful in their later careers.

7. Gifted children average above the general child population in character and personality tests and trait ratings. They are more stable emotionally and better adjusted socially.

8. Up to age 35 the gifted group shows a normal or below normal incidence of serious personality maladjustment, insanity, delinquency, alcoholism, and homosexuality.

9. Children of very high I.Q. (above 170) do better at school than lower testing individuals; they are not more prone to serious maladjustment; and they are more successful vocationally.

10. As adults, the gifted group is well above the average college graduate in vocational achievement. They marry more often than other college graduates and marital adjustment is better. The divorce rate is lower.

11. There is a tendency for the I.Q.'s of the offspring of gifted adults to regress toward the mean, but the mean I.Q. (127) of the children is much higher than that of average children (I.Q. 100).

REFERENCES

1. Terman, L. M., and Oden, M. H.: *The Gifted Child Grows Up*, Stanford University Press, Stanford, Cal., 1947.
2. MacMeeken, A. M.: *The Intelligence of a Representative Group of Scottish Children*, London, University of London Press, 1939.

Comments on Current Literature

AUREOMYCIN AND PERTUSSIS

THE severity of pertussis varies considerably from year to year, and also from patient to patient. It is generally agreed, however, that the infection may be a serious disease, especially when it occurs in infants under the age of 6 months. According to Gordon and Almaden¹ the mortality rate in pertussis for the United States is 2.3 per cent, and for the state of Arkansas in 1947 it was 3.3 per cent. These authors have stressed the age factor, pointing out that in their analysis of fatalities due to pertussis 40 per cent of the deaths occurred in infants under 3 months of age and 68.5 per cent occurred in patients under 6 months of age.

In general, therapy of whooping cough has not been satisfactory. Prevention of the disease by active immunization is highly desirable and has gained popularity in recent years. Nevertheless, pertussis still occurs and improved therapeutic methods are needed. While the development of hyperimmune human antipertussis serum has been accepted as a therapeutic advance, and more recently the value of streptomycin has been demonstrated in a small series of patients,¹ a specific and effective therapeutic agent in the treatment of pertussis is still an urgent need.

Recently Joseph A. Bell, Margaret Pittman, and Byron J. Olson (May 13, 1949, issue of *Public Health Reports*)² demonstrated the therapeutic effectiveness of aureomycin in experimental animals and reported preliminary clinical trials. White Swiss mice were inoculated intracerebrally with suspensions of *Hemophilus pertussis*, and then treated with aurcomycin. By varying the approximate number of organisms in the intracerebral inoculum, the dosage of antibiotic, the time intervals of antibiotic administration, and the duration of treatment, these investigators attempted to gain a general idea of the most satisfactory treatment regime. They concluded on the basis of these observations that aureomycin is an effective agent in the treatment of *H. pertussis* infection of white Swiss mice, and that a "treatment regime of small doses given at frequent intervals over a period of several days was more effective than larger doses given singly or at infrequent intervals for a few days." Encouraged by the results of the experimental studies in mice, this group undertook an evaluation of the therapeutic effectiveness of aureomycin in human pertussis. Since members of this team have been engaged in a study of pertussis in Norfolk, Va., for a period of ten years, it would seem that even a preliminary evaluation of the antibiotic in patients in that community might be of real statistical value.

The treatment schedule was designed for home use, and a total of 20 patients was treated. Aureomycin was administered by mouth in sweet cherry syrup, beginning on the second to the seventeenth day following onset of the paroxysmal cough. In the first eight cases a total dose of 0.5 Gm. aureomycin per kilogram of body weight was given in divided doses over a period of four days. The remainder of the patients received the same total dosage distributed over an eight-day period. When vomiting occurred following administration, the dose was repeated. Patients ranged in age from one month to 6 years. Since paroxysmal coughing often attended by whooping and vomiting is considered a characteristic clinical manifestation of pertussis, the duration, frequency, and

intensity of the paroxysmal cough were the chief criteria for evaluating the effect of the therapeutic agent. Comparing the duration of paroxysmal cough in the twenty treated cases with 380 untreated controls (Bell and associates, Table 5), the authors concluded that "... aureomycin given orally in apparently nontoxic doses shortened the clinical course of the disease." "In only a few," however, "particularly the cases treated early, was the response ... dramatic in the sense that complete recovery immediately followed a few days' treatment."

TABLE 5. DURATION OF PAROXYSMAL COUGH IN TREATED AND UNTREATED CASES OF PERTUSSIS²

	INTERVAL ONSET PC TO TREAT- MENT (DAYS)	YEAR OF OCCUR- RENCE	TOTAL CASES	DAYS DURATION OF PAROXYSMAL COUGH			
				< 20	20-29	30-39	40- PLUS
Untreated cases -----	{ 1938-42 1942-47	1938-42 1942-47	165 215	11 14	25 29	42 47	87 125
Total -----			380	25	54	89	212
Aureomycin treated cases -----	{ 9-10 11-17	1949 1949	7 13	7 0	0 10	0 2	0 1
Total -----			20	7	10	2	1
Expected number of treated cases if distributed like untreated cases -----			20	1	3	5	11

While the results of this preliminary report cannot be accepted as proof that aureomycin is a specific for *H. pertussis*, one gains the impression that this antibiotic seems to have a beneficial effect on the clinical course of the disease. In these preliminary trials the lack of adequate controls, which would have involved the treatment of alternate cases of similar severity in the same epidemic, is a reasonable objection. It must be recognized that the role of secondary bacterial invaders is of paramount importance in the clinical evaluation of any therapeutic agent in the treatment of pertussis.

If aureomycin or other antibiotics administered by mouth should prove effective in the treatment of pertussis, home care of a large number of patients will certainly improve the mortality statistics in this important pediatric disease.

RUSSELL J. BLATTNER.

REFERENCES

1. Gordon, Vida H., and Almaden, Philip J.: Streptomycin Therapy for Pertussis, *J. Pediat.* 34: 279, 1949.
2. Bell, Joseph A., Pittman, Margaret, and Olson, Byron J.: Pertussis and Aureomycin, *Pub. Health Rep.* 64: 589, 1949.

News and Notes

The following communication regarding the Sixth International Pediatric Congress to be held at Zurich in July, 1950, has been received from Prof. G. Fanconi, president of the Congress:

During the Fifth International Pediatric Congress in New York a Committee of Seven (composed of Professors R. Debré, Paris; Gomez Santos, Mexico; H. F. Helmholz, Rochester, Minn., former president; Emmett Holt, New York, Secretary-General; Maslow, Leningrad; A. Moncrieff, London, and G. Fanconi, Zurich, who was elected President of the Sixth International Pediatric Congress), met in order to draw up rules for the constitution of an international pediatric association (I.P.A.).

Pending the acceptance by the International Congress of 1950, this committee decided the following:

1. To establish a list of the various national Pediatric Societies as well as of their presidents and possibly their members. Dr. Fanconi, as well as Professor E. Holt (Bellevue Hospital, 26th St. and 1st Ave., New York, N. Y.), ask you kindly to send them the required information.
2. To create an international reference journal of pediatrics.
3. To give advice to other organizations concerned with child health and welfare.
4. To organize international regional meetings in order to discuss special problems of immediate importance.

Until the coming Congress in 1950 the official communications of the I.P.A. will be published in six languages in the regular numbers of *Helvetica Paediatrica Acta*. These will be sent free of charge to the presidents of the national societies.

Dr. Fanconi requests that the various national pediatric societies kindly communicate to him, as soon as possible, suggestions for the main subjects to be discussed at the Sixth International Pediatric Congress.

Book Reviews

The Premature Infant. Julius H. Hess, M.D., and E. C. Lundeen, R.N., Philadelphia, 1949, J. B. Lippincott Company, 381 pages. Price \$6.00.

This second edition clearly reflects the increasing medical and public health interest in the premature infant which has been developing in recent years. Dr. Hess, the senior author, has been a pioneer in the field and was responsible for the establishment of the premature infant station in the Michael Reese Hospital in 1922, which led to the "Chicago plan" for city-wide care of the premature infant, and, in turn, to the state plan for Illinois, which has served as a "pilot" for state-wide plans now being established in other commonwealths. Miss Lundeen is the supervisor of the hospital station and has contributed much to the text, as it is generally recognized that the nursing care of the premature infants is of equal if not greater importance than the medical. Theoretically, it makes an ideal team for a text on the care of the premature infant, and in this instance, the authors have come through with glowing colors. The reader distinctly gets the feeling that the text is based on long and developed personal experience with the premature infant and is not a compilation. The material is presented in a direct and practical manner and the new edition includes the recent developments in chemo- and antibiotic therapy. It can be highly recommended as a practical, thorough, and complete text on the care of the premature infant and his medical and nursing problems.

How to Become a Doctor. George R. Moon, Philadelphia, 1949, The Blakiston Company, 131 pages. Price \$2.00.

This book by the Examiner and Recorder of the University of Illinois Colleges of Medicine, Dentistry, and Pharmacy, should be of great help to young men and women who are planning or thinking of becoming a doctor. It is based on an experience of twenty years in which the author has interviewed some 20,000 prospective medical students. The author discusses the quantitative requirements for admission to a medical school and the selection of a college. A detailed but brief summary of the admission requirements to each approved school is then given. The application form is discussed and how it should be completed. The Medical College Admission Test and the way the "Committee on Admissions" functions in a medical school is the theme of the next chapter. There is a brief chapter on success and failure and on the medical course. In subsequent chapters dentistry and pharmacy are discussed.

We know of no other book which covers a similar field, and it should be carefully read by every boy or girl who has a medical career in mind. Throughout the text the author gives sane and sound advice to the prospective medical student based on his years of experience. It should help many young people avoid a lot of disappointment as less than one of three applicants each year can be admitted to the study of medicine.

Poliomyelitis. Papers and Discussions Presented at the First International Poliomyelitis Conference, Philadelphia, 1948, J. B. Lippincott Company, 360 pages. Price \$5.00.

This volume contains the papers and discussions presented at the International Poliomyelitis Conference held in New York in July, 1948, which was sponsored by the National Foundation for Infantile Paralysis. A careful reading of the papers and discussions which followed confirms the feeling of those present at the conference that it set a high mark for an international conference. Practically every phase of poliomyelitis and its problems is presented and discussed by authorities in their respective fields. All in all it contains as important a group of essays on poliomyelitis as could have been obtained. Further, the discussions are keen and to the point and have been unusually well edited. There are twenty essays on primary presentation on such subjects as poliomyelitis as a world problem by A. B. Sabin, four on the early stage, such as the pathologic anatomy by David Bodian and treatment by John A. Anderson, four on the convalescent stage, three on bulbar poliomyelitis, three on the problems of immunology and chemotherapy, and three on public health aspects. Each paper was discussed by a number of well-selected workers in the particular field and subject under discussion. The absence of disagreement in the discussions as a whole is quite striking. It is the most valuable discussion of our present-day knowledge of poliomyelitis and its problems which exists and will be of greatest help to all who in one way or another are concerned with or interested in the disease. It is one of the most important contributions that the National Foundation has made, and great credit must go to the general chairman of the conference, Dr. Hart E. Van Riper, for bringing together leading clinical and laboratory authorities from all over the world to share their knowledge. The volume itself, from the printing standpoint, is above average, and obviously much care and thought have been given by the publishers to the format.

Rheumatic Fever: Nursing Care in Pictures. Sabra S. Sadler, R.N., B.S., Philadelphia, 1949, J. B. Lippincott Company, 151 pages.

This is an excellent handbook primarily intended for the public health nurse who has to instruct parents in the daily home care of the patient with rheumatic fever. The various nursing procedures are very simply and completely outlined. In addition, these written instructions are supported by excellent photographs which demonstrate the home nursing techniques.

GOLDRING.

Editor's Column

GASTRIC SUCTION TO PREVENT ASPHYXIA NEONATORUM IN INFANTS DELIVERED BY CESAREAN SECTION

ELLIS, White, and Pfeffer* have introduced the novel procedure of gastric suction to prevent some of the respiratory illness which frequently affects newborn infants of mothers delivered by cesarean section. It is common knowledge that respiratory difficulty is more common after cesarean section than after delivery in the normal way. Respiratory embarrassment which takes place immediately after birth may be accounted for by the use of depressing drugs, anoxic injury to the infant, the aspiration of amniotic fluid, etc. More difficult to explain is the respiratory distress which begins some hours after birth. One mechanism here is the packing of inhaled debris against the alveolar walls. This material at first lies loosely distributed in the alveolar spaces but with each successive inspiration the aspirated debris is pressed against the alveolar walls until a membrane is formed rendering them increasingly impervious.†

The authors present evidence of another mechanism leading to the delayed onset of respiratory difficulties of an obstructive nature with inspiratory retraction, dyspnea, tachypnea, and cyanosis. Suspecting that the aspiration into the lungs of amniotic fluid which had been swallowed at or shortly before birth and then regurgitated might be a factor, they withdrew the gastric contents immediately after delivery. Gastric suction was repeated at three-hour intervals for twelve hours. Ten to 20 c.c. of fluid were usually obtained at the initial aspiration, but in some instances over 30 c.c. were obtained.

Twenty-five infants of diabetic mothers, delivered by cesarean section, were treated in this way. Of these only four showed respiratory symptoms. These were mild and were present at the time of birth. In a control group of infants of diabetic mothers, also delivered by cesarean section but not subjected to gastric suction, six had respiratory difficulties at birth and nine developed symptoms later on. Moreover, the severity of respiratory embarrassment was much greater in the control group. Five infants of diabetic mothers delivered by low forceps had smaller amounts of fluid in the stomach. Only one of these had respiratory difficulty immediately after birth.

In twelve infants of nondiabetic mothers delivered by cesarean section amounts of fluid varying from 6 to 28 c.c. were aspirated from the stomach. Two of the babies had respiratory symptoms at birth. None developed difficulty later on. Fifteen babies of nondiabetic mothers delivered by low forceps had very small amounts of fluid in the stomach.

It appears, then, that babies delivered by cesarean section, whether from diabetic or nondiabetic mothers, frequently have large amounts of fluid in the stomach, in some instances approaching what is generally considered the gastric

*Ellis, S. S., White, P., and Pfeffer, W.: Gastric Suction: A Proposed Additional Technique for the Prevention of Asphyxia in Infants Delivered by Cesarean Section. *New England J. Med.*, 210: 523, 1939.

†Marber, S., and Sweet, L. K.: Amniotic Fluid Contents in Lungs of Infants. *Am. J. Dis. Child.*, 42: 1372, 1931.

capacity of the newborn infant (30 to 35 c.c.). This is of interest in relation to the observations of Russ and Strong,* who found increased amounts of material in the tracheas of infants delivered by cesarean section.

In view of the more favorable neonatal course of infants who received gastric suction, Gellis, White, and Pfeffer propose that this procedure be carried out routinely in deliveries by cesarean section, in addition to the measures now commonly employed for the prevention of asphyxia.

AUREOMYCIN AND PERTUSSIS

PERTUSSIS holds about the first place in the group of infectious diseases for which there is no satisfactory therapy. Some evidence has been presented in THE JOURNAL during the last year which indicates that further trials with streptomycin are warranted. Recently Dr. Bell of the Public Health Service and his associates† have shown that aureomycin may have value and needs further study. A similar report was made a week previously by Dr. Bradford of Rochester, N. Y., at a meeting of the American Pediatric Society; it will be published in a subsequent issue of THE JOURNAL.

Bell and his associates found that aureomycin in nontoxic doses delayed or prevented death in mice infected intracerebrally with *Hemophilus pertussis*. Small doses over a period of eight days were more effective than large doses given over a short period of time. Preliminary clinical trials in twenty cases of pertussis apparently shortened the clinical course of the disease. In only a few cases treated early was there a "dramatic response." The authors make no extravagant claims but only that "further clinical trials are necessary to establish its value for general treatment of clinical pertussis." An extensive controlled clinical trial should certainly be made on the basis of these early preliminary reports.

EXCERPTA MEDICA

MANY pediatricians, we find, are unfamiliar with *Excerpta Medica*, an extensive medical abstract service published in Holland by a nonprofit organization and approved by UNESCO. It is in fifteen sections and printed in English. Section VII, Pediatrics, contains about 250 abstracts taken monthly from medical journals published throughout the world. There are about 600 pages, including an index, in the annual volume. Each of the fifteen sections may be subscribed to separately, Section VII costing \$15.00 a year. The Williams & Wilkins Company of Baltimore are the agents for the United States. The abstracts are thorough and well written. For the Pediatrics section there are six Americans on the present editorial board of twenty-two. Some 3,500 abstract writers from more than forty countries are cooperating on the fifteen sections. It is far superior to the "Referate" sections of the German pediatric journals upon which we largely depended before the war for an abstract service. *Excerpta Medica* is now in its third year.

*Russ, J. D., and Strong, R. A.: La Asfixia en el Recien Nacido. *Bul. Med. del Hosp. Infantil* 5: 27, 1948. Idem. Asphyxia of Newborn Infants. *Am. J. Obst. & Gynec.* 51: 613, 1946.

†Bell, Pittman, and Olson, *Pub. Health Rep.* 64: 589, May 13, 1949.



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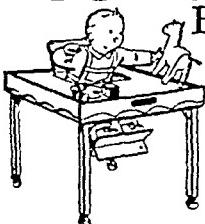
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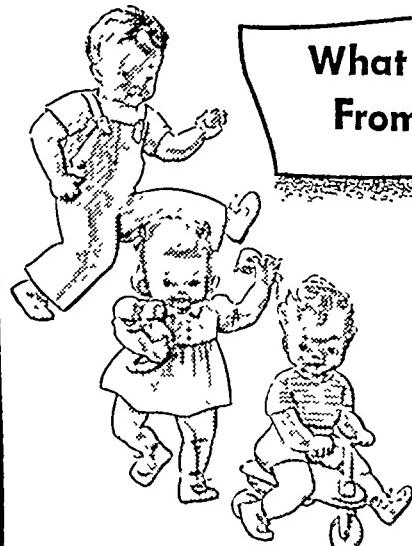
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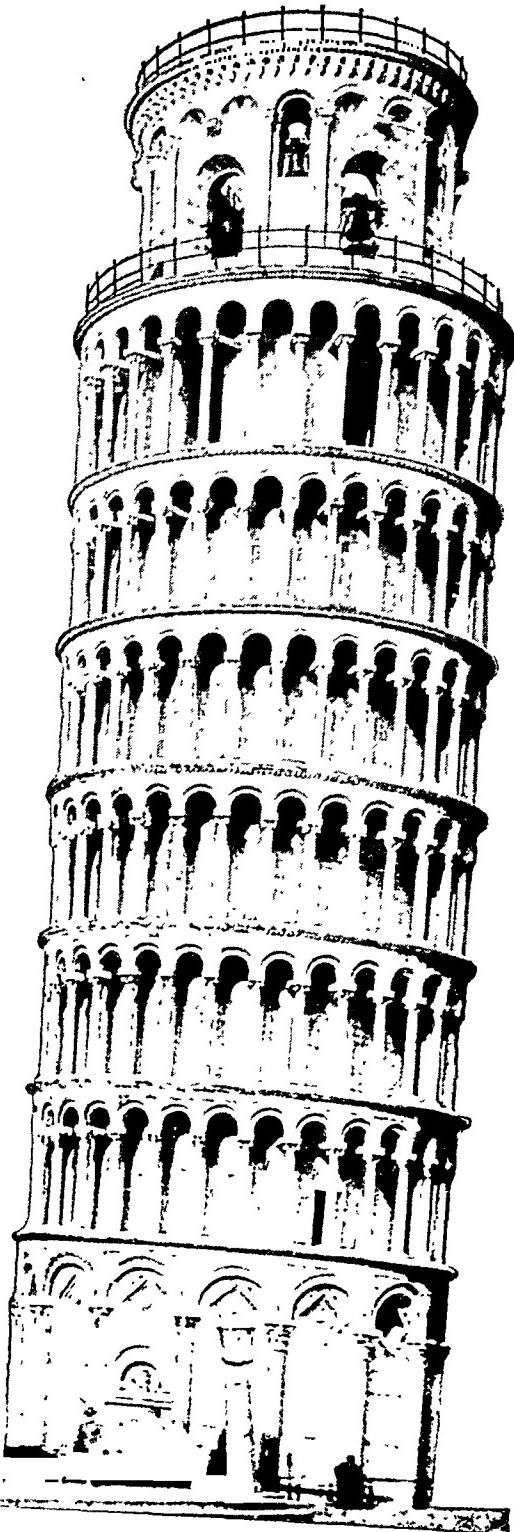
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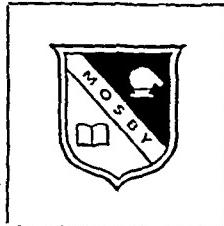
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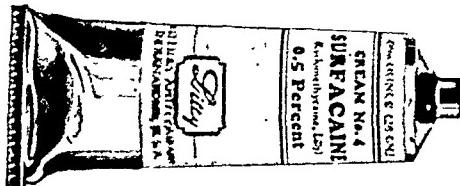
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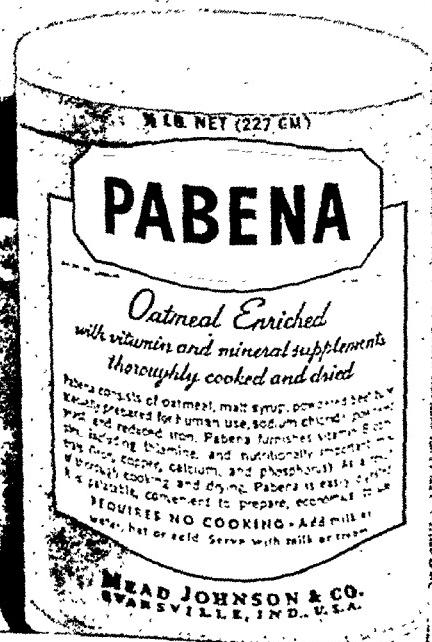
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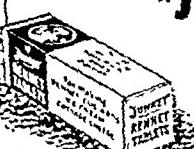
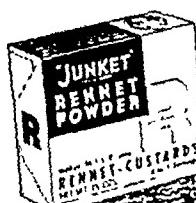
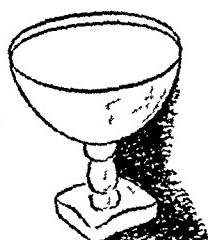
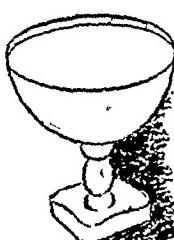
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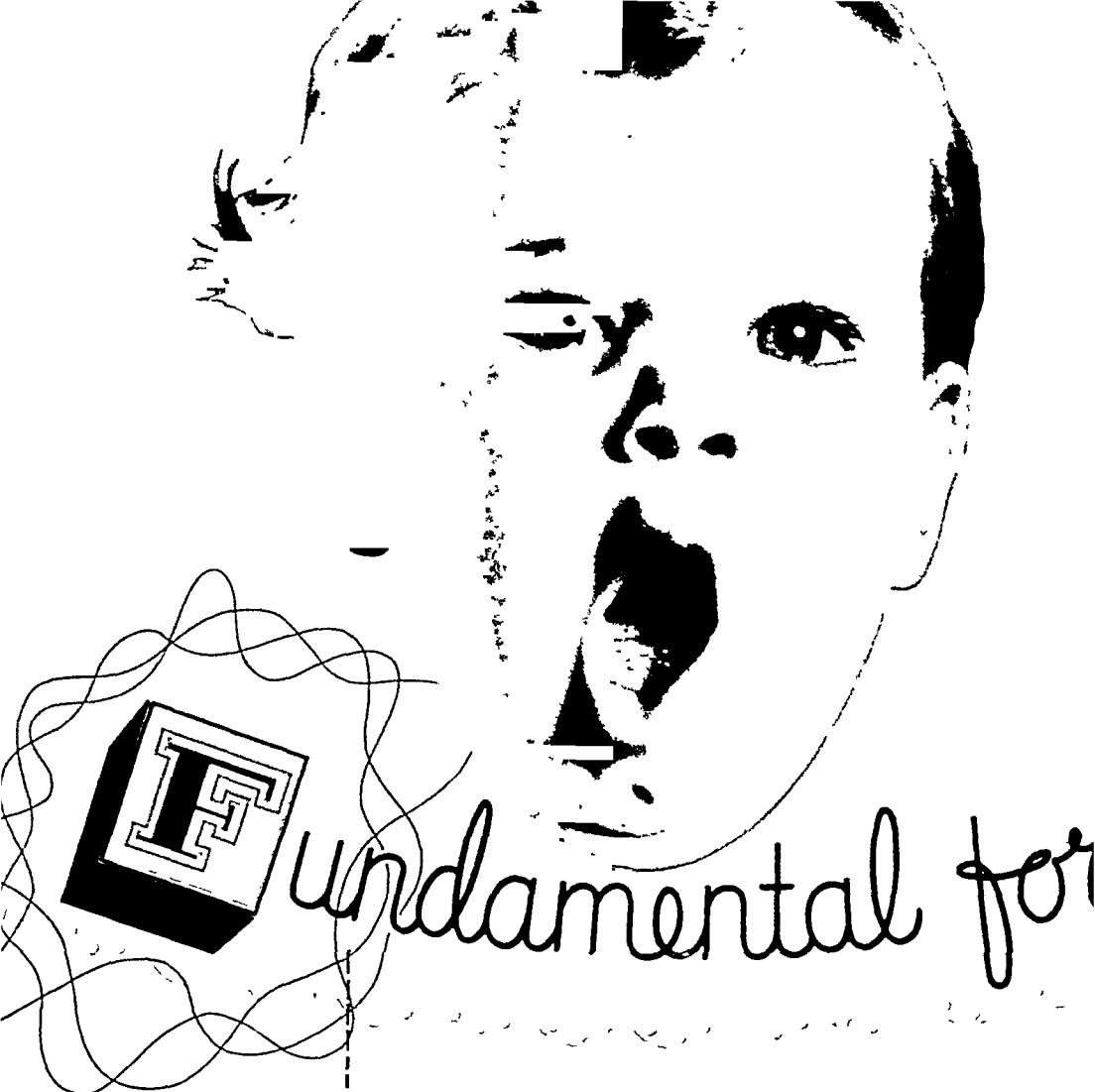
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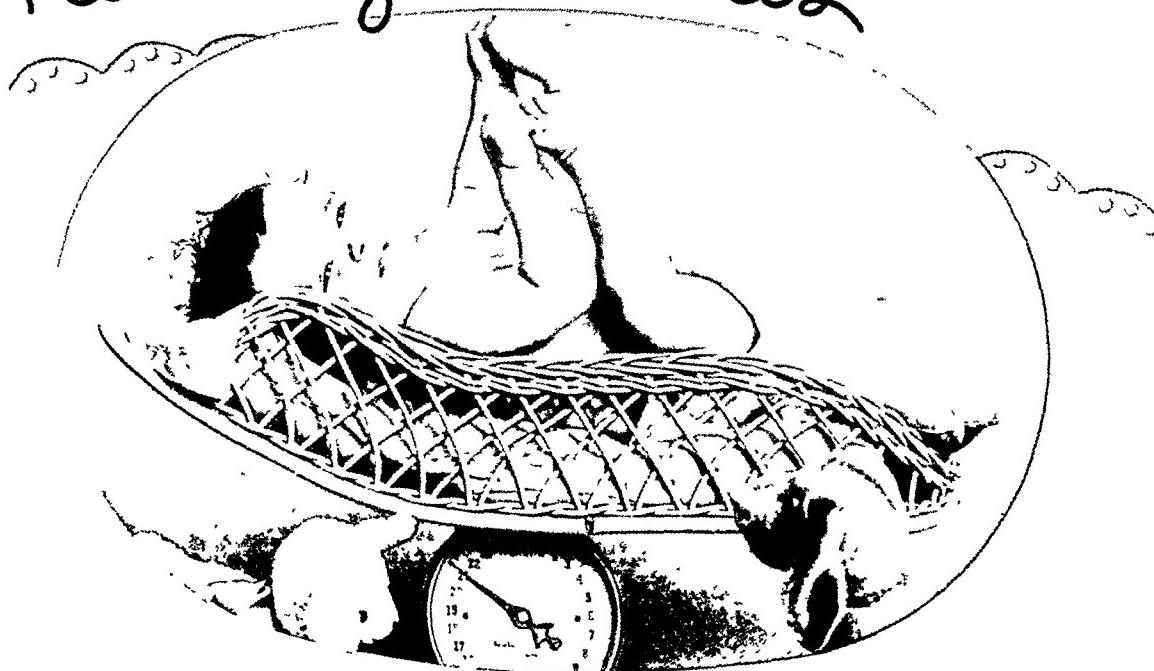
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1. Marriott, W. McK., Infant Nutrition, St. Louis, C. V. Mosby Co., 1941, p. 63.

2. Ibid. p. 96.

3. Kugelman, I. N., Newer Nutrition in Pediatric Practice, Philadelphia, J. B. Lippincott Co., 1940, p. 633.

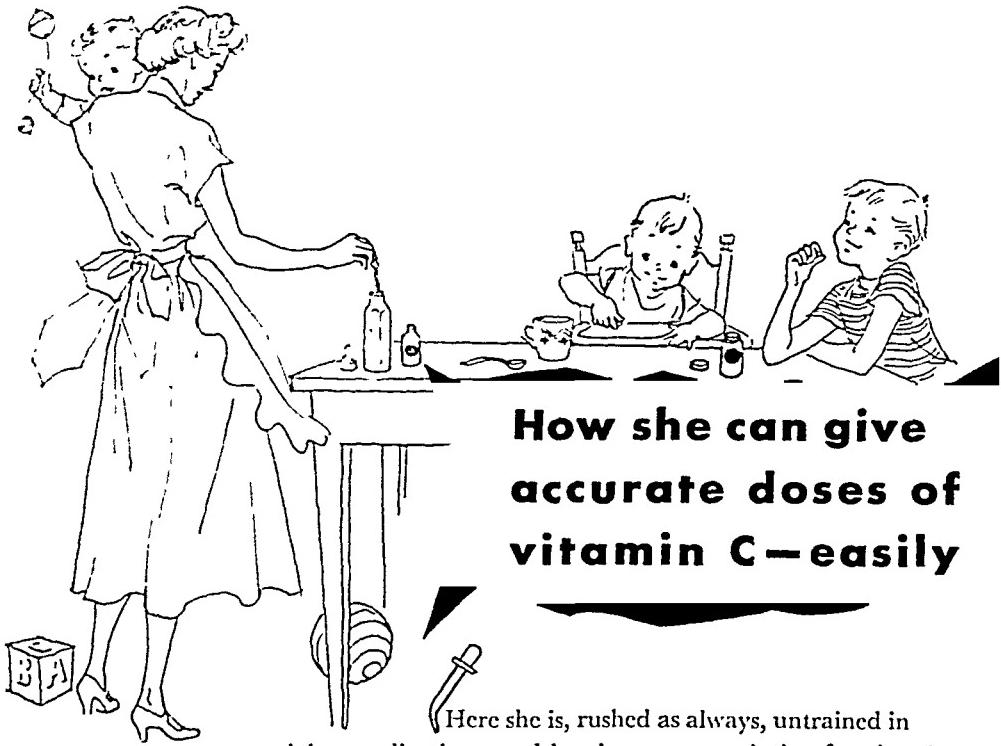
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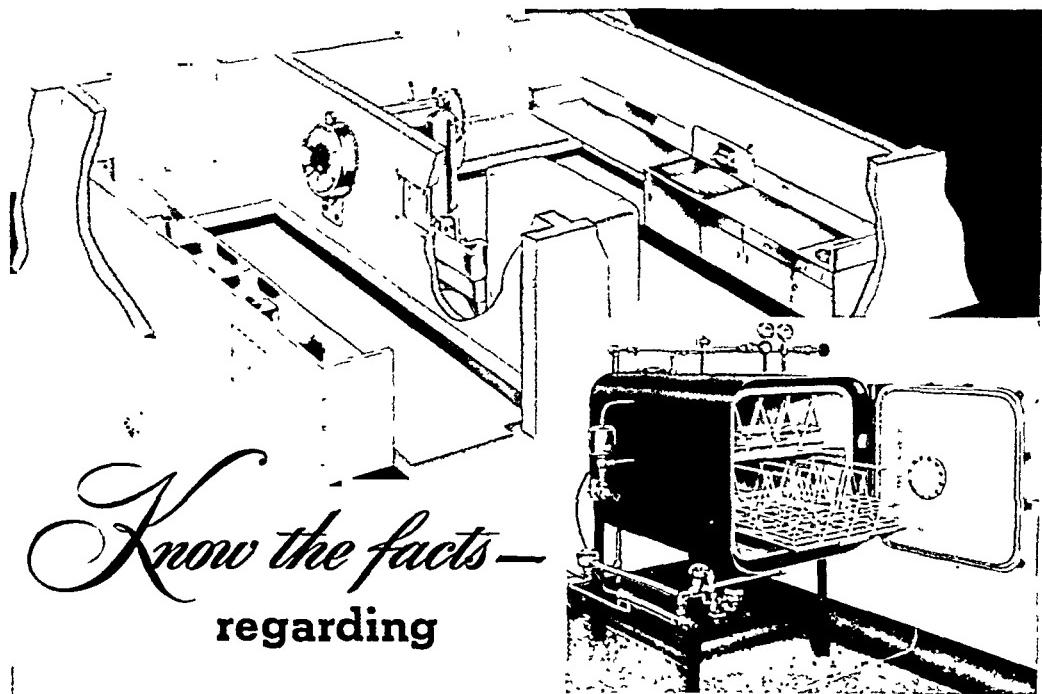
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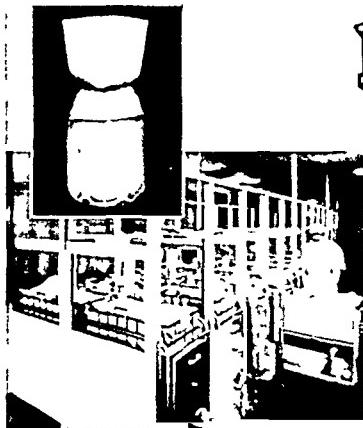
SIMILAC DIVISION
M & R DIETETIC
LABORATORIES, INC.
COLUMBUS 16, OHIO





*Know the facts—
regarding*

SAFE MILK FORMULA PROCEDURES



OUR PLANNING SERVICE is available to aid you in establishing an approved technique and in the planning of a modern installation best suited to your available facilities.

1 Based upon the many years devoted by our Research and Technical Staffs to the development of techniques and equipment designed to insure the efficient preparation of infants' formulas, "American" strongly recommends the NON-PRESSURE method of terminal heat treatment because of its safety features and mechanical simplicity.

2 Functionally, American equipment is readily adaptable to all approved techniques... whether a non-pressure or pressure method is preferred by the hospital.

FACTS ON THIS TIMELY SUBJECT are thoroughly evaluated in the new edition of "The American Milk Formula Laboratory Service," a comprehensive volume incorporating the most recent recommendations of authoritative groups relating to the establishment of safe milk formula procedures in the hospital—**WRITE FOR YOUR COPY TODAY.**



AMERICAN STERILIZER COMPANY
ERIE, PENNSYLVANIA

DESIGNERS AND MANUFACTURERS OF SURGICAL STERILIZERS, TABLES AND LIGHTS

Kanana Banana Flakes

Reg. U. S. Pat. Off.

In the management of infantile diarrhea of non-specific origin

The effectiveness of banana therapy in the management of infantile diarrhea of non-specific origin has led to widespread use of KANANA BANANA FLAKES for such cases. The following dietary regimen is suggested.

1. At the outset of diarrhea, one tablespoon of KANANA BANANA FLAKES per pound of body weight per day for the first 48 hours on the following schedule:

Every 2 hours during the day and every 4 hours during the night.

2. For the next 48 hours place the infant on a transition diet of skimmed milk, KANANA BANANA FLAKES and water.

Administer KANANA BANANA FLAKES in the following proportions:

Bottle fed infants: 1 tablespoon of Flakes to 4 ounces of boiled water or skimmed milk.

Spoon fed babies: 1 part of Flakes to 3 parts of liquid.

KANANA BANANA FLAKES are made by extracting the water from sun-ripened bananas which are rich in desirable vitamins, proteins and sugars. *The diarrhea patient need never wait for bananas to get ripe.*



The 5½ oz. can contains 20 six inch size bananas costing less than fresh fruit.

Kanana Banana Flakes cost less than fresh fruit



Write for free samples

KANNENGIESSER & COMPANY

76 NINTH AVENUE • NEW YORK 11, N. Y.

Distributed in Canada by
J. T. WAIT COMPANY, Limited, 760 St. Antoine Street, Montreal, Canada

July, 1949

Page 9

STABILITY



DAPTA
means
full
vitamin
potencies

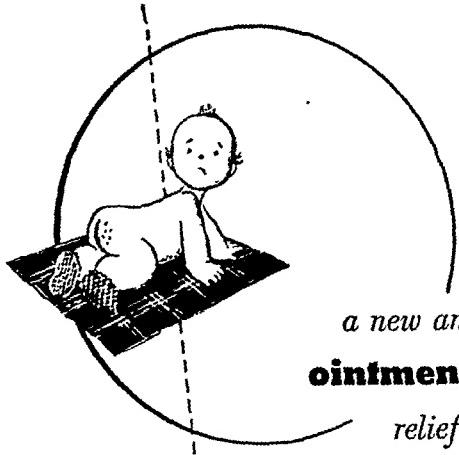
Dapta is stable, as confirmed by repeated assays. Therefore, you can be certain of the full vitamin intake prescribed when you specify Dapta for infants and children.

Dapta is nonoily, assuring efficient utilization. It is pleasant-tasting, readily miscible with milk and other foods.

Recommended dosage: Infants, 0.5 cc. daily; children 1 to 6, 1 cc. daily.



WYETH INCORPORATED • PHILADELPHIA 3, PA.



a new antihistamine
ointment for
relief of pruritus

Thephorin, the new antihistamine with minimal side reactions, is now available in 5 percent ointment for effective relief of pruritic and allergic skin disorders. In most cases Thephorin Ointment quickly relieves the discomfort of atopic dermatitis, chronic contact dermatitis, lichenified eczema, pruritus ani, pruritus vulvae, and other pruritic complaints. 1½ oz. tubes and 1 lb. jars.

HOFFMANN-LA ROCHE INC. • NUTLEY 10 • N. J.

Thephorin®
'Roche' *Ointment*

brand of phenindamine

True in '38

“Because of the convenience, smaller adequate dose, and better tolerance, the trend is toward the use of ferrous sulfate . . .”

*Sielke, E.L.: Rhode Island M.J.
21:61 (April) 1938*

True in '48

“No iron preparation has proved superior to ferrous sulfate, with respect either to economy or efficacy.”

*Emerson, C.P., Jr.: M.Clin. North America
32:1264 (Sept.) 1948*

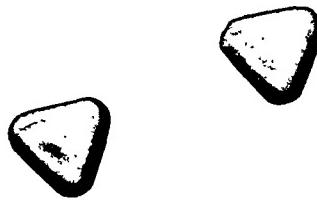
and True Today

There are many iron preparations, but only Feosol Tablets provide ferrous sulfate with the special, S.K.F.-developed vehicle and coating that—

1. prevent oxidation of the ferrous sulfate into the inferior ferric form
2. assure prompt disintegration in the acid medium of the stomach and upper duodenum, where iron absorption is best.



Each Feosol Tablet contains 3 grains exsiccated ferrous sulfate—the equivalent of approximately 5 grains crystalline ferrous sulfate.



Feosol Tablets



the standard iron therapy

*Smith, Kline & French Laboratories
Philadelphia*



after tonsillectomy...

"For excessive pain, **Aspergum**
chewed before mealtime
is effective . . . **

DILLARD'S
aspergum

SALIVARY ANALGESIA

Contains 3½ grains of aspirin in a pleasantly flavored chewing gum base—particularly suitable for administering aspirin to children and to patients who have difficulty swallowing tablets.
Ethically promoted.

*Hollender, A. R.: Office Treatment of the Nose, Throat & Ear, Chicago, The Year Book Publishers, Inc., 1943, p. 316.

WHITE LABORATORIES, INC.,
Pharmaceutical Manufacturers,
Newark 7, N. J.

Citrus fruits and juices... **to help corral top growth and vigor!**

The importance of the daily ingestion of liberal quantities of natural vitamin C, to help insure optimal growth and development in the young,¹ is now widely recognized. And there are few better ways of providing this essential nutritional intake than by urging mothers to administer generous quantities of Florida citrus fruits and juices—either fresh, canned, concentrated or frozen—every day. Children in sickness and health usually relish the delicious refreshing taste.

These richly-nutritious fruits are, of course, brimful of easily assimilable natural fruit sugars for much needed child-energy—and their outstandingly high vitamin C content together with other nutrients*, contribute significantly to the maintenance of tissue integrity,³ improved calcium utilization, and enhanced bodily vigor, stamina, and resistance to disease.²

**FLORIDA CITRUS COMMISSION
Lakeland, Florida**

references:

1. Jeans, P. C. and Marriott, W. M.: *Infant Nutrition*, Mosby, 4th ed., 1947.
2. Rose, M. S.: *Rose's Foundation of Nutrition*, rev. by MacLeod and Taylor, Macmillan, 4th ed., 1944.
3. Sherman, H. C.: *Chemistry of Food and Nutrition*, Macmillan, 7th ed., 1946.



*Citrus fruits—
among the richest
known sources of
vitamin C—also
contain vitamins
A, B₁ and P,
readily assimilable
natural fruit
sugars, and
other factors,
such as iron,
calcium, citrates
and citric acid.

FROM NATURE'S
TREASURE CHEST...



of health
and sunshine

FLORIDA

Oranges • Grapefruit • Tangerines

Articles to appear in early issues of
The JOURNAL OF PEDIATRICS

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By Herman Anfanger, M.D., Murray H. Bass, M.D., Robert Heavenrich, M.D., and John J. Bookman, M.D., New York, N. Y.

THE CEPHALIN CHOLESTEROL FLOCULATION TEST IN INFANTS AND CHILDREN.

By C. W. Biedel, M.D., Bremerton, Wash.

AN EXPERIMENT IN SEX EDUCATION AT A BOY'S SUMMER CAMP.

By Lawrence M. Shapiro, M.D., New York, N. Y.

FURTHER STUDIES ON ORAL PENICILLIN IN THE PROPHYLAXIS OF RECURRENT RHEUMATIC FEVER.

By Martin M. Maliner, M.D., Sol. Darrell Amsterdam, M.D., and C. C. Arreechie, M.S., Brooklyn, N. Y.

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By Harry Bakwin, M.D., New York, N. Y.

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By James B. Gillespie, M.D., and A. Jerome Hurter, M.D., Urbana, Ill.

ORAL PENICILLIN FOR CHILDREN WITH RHEUMATIC FEVER.

By Jesse W. Hofer, Ph.D., M.D., Chicago, Ill.

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By Joseph Schwartzman, M.D., and Marion Cerone, R.N., New York, N. Y.

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By David I. Arbuse, M.D., Morton B. Cantor, M.D., and Paul A. Barenberg, M.D., New York, N. Y.

PYLORIC STENOSIS IN ONE OF IDENTICAL TWINS.

By Roy F. Garrison, M.D., Kansas City, Kan.

FEEDING PREMATURE INFANTS.

By James W. Bruce, M.D., Louis J. Hackett, Jr., M.D., and John E. Bickel, M.D., Louisville, Ky.

THE FULMINANT FORM OF EPIDEMIC HEPATITIS IN A TWO MONTH OLD INFANT.

By First Lieutenant Robert R. Williams, and Captain Ben Gaber, Medical Corps, Army of the United States.

SUMMER SORROWS

poison ivy
& CO.

poison ivy is
probably the
most prolific
summertime source
of pruritus

AS AN AID TO AVOIDANCE

of dermatitis venenata, the famous
CALMITOL "Ivy Leaf" * reproduces an exact
cut-out of the *rhus* leaf and gives some
simple criteria for plant identification.

AS AN AID TO TREATMENT

CALMITOL affords swift, sustained
and safe control of itch caused by
dermatitis venenata or of any other
origin. Completely free from
dangerous drugs such as phenol,
cocaine and cocaine derivatives,
CALMITOL effectively and safely
blocks the pruritic impulse at
its point of origin through the anti-
pruritic action of camphorated chloral,
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CALMITOL

*The CALMITOL "Ivy Leaf" may be obtained,
as a professional service, in quantities suitable
for practitioners, school and company physicians
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Thos. Leeming & Co., Inc.

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in pediatrics... where minor infections are under consideration, Sulfadiazine is the drug of choice... in

most of the infections for which it is given, its antibacterial effect is on a par with that of penicillin
(Bakwin, H. New York St. J Med 49:391-396, 1949).



in penicillin-insensitive infections...

a combination of penicillin and sulfadiazine is much more effective in infections with hemophilus influenza (Gottlieb, B., and Forsyth, C. C.: J A M A 135:740, 1947).

The choice remains



in the home... when bacteriostasis is required, the

sulfonamides are still the drugs of choice (Oettinger, Jr., L., and Cranheim, G. Am Pract 2:526-529, 1948)

GLUCO-SULFADIAZINE

For safer sulfonamide medication, prescribe Donley-Evans'

GLUCO-SULFADIAZINE in liquid form for oral use.

GLUCO-SULFADIAZINE—a suspension of Sulfadiazine in a vehicle of highly purified sodium lactate and glucose assures renal safety. GLUCO-SULFADIAZINE is notable for positive uniformity, thus providing higher blood levels (than tablet form) and more rapid response. Exceptional palatability and ease of administration facilitate sulfonamide therapy in infants and children.

GLUCO-SULFADIAZINE

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GLUCO-SULFANILAMIDE

GLUCOSulfas

A Triple Mixture

DONLEY-EVANS & COMPANY



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The Journal of Pediatrics



Something NEW for baby from the Convolvulaceae family!

Before you reach for the dictionary—it's Gerber's Strained Sweet Potatoes! Now specially prepared for babies!

New store-house of nutrition! One container of Gerber's Sweet Potatoes furnishes twice the recommended daily infant allowance of Vitamin A, plus significant amounts

of essential iron and Vitamin C.

Golden goodness — all fiber-free, satin-smooth! For like all Gerber's, Starting Cereals to Junior Meats—the "Sweets" have Perfected-Texture.

FREE SAMPLES OF 3 CEREALS, plus analyses of the new Sweet Potatoes. Write Gerber's, Dept. 277-9 Fremont, Mich.

Gerber's
BABY FOODS
Fremont, Mich.



Babies are our business... our only business!

Tested and proven by doctors, nurses and mothers in over 2 million feedings...



THE Shellie NURSER

with pre-sterilized, disposable bottles...

"the nearest thing to breast feeding"

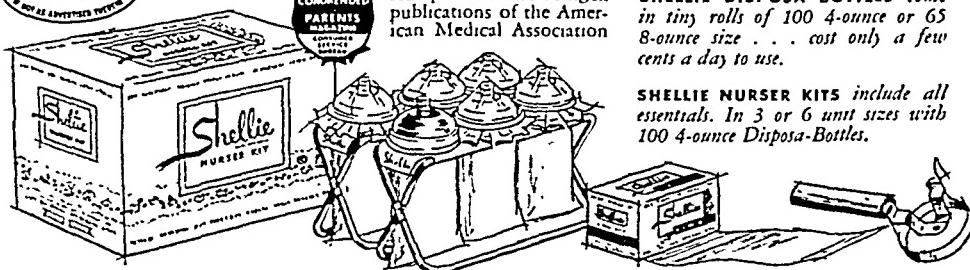
- Flexible Disposa-Bottles of soft-yet-strong plastic collapse as baby nurses—there's no vacuum to cause painful air colic. Natural-Action Nipples—possible only with the vacuum-free Shellie Nurser—can't collapse, and their breast-like shape and softness encourage natural sucking exercise. So simple and safe to use—the day's bottle drudgery is over in one-fourth the usual time!



Accepted for advertising in publications of the American Medical Association

SHELLIE DISPOSA-BOTTLES come in tiny rolls of 100 4-ounce or 65 8-ounce size . . . cost only a few cents a day to use.

SHELLIE NURSER KITS include all essentials. In 3 or 6 unit sizes with 100 4-ounce Disposa-Bottles.



If not yet available in your vicinity, write to Shellmar Products Corporation • Mt. Vernon • Ohio

Summer Comfort...

JUMPING-JACK protection

Little feet are cool, free, yet well protected in Jumping-Jack summer shoes.
Heels snugly cradled, foot kept well centered, yet Jumping-Jack flexibility permits complete foot freedom.



JUMPING-JACKS
FLEXIBLE SHOES FOR HARD WEAR

FOR ALL CHILDREN 6 MONTHS TO 4 YEARS

AVANCE-BRISTOL SHOE COMPANY, INC.
ROCHESTER, NEW YORK
HOME OF THE MISSOURI JACKSON WHEATON, MAINE
TOMMY TEE SHIRT, THE SPAN, LIMITED, PRESTON, ONTARIO



In
infant allergy to
cow's milk lactalbumin

Meyenberg **EVAPORATED GOAT MILK**

gives
prompt,
proven
relief

PRESCRIBE MEYENBERG, the original evaporated goat milk, for prompt relief from the colic, diarrhea or vomiting due to cow's milk allergy. When allergy is indicated, or in borderline cases when sensitivity to cow's milk lactalbumin is suspected, prescribe Meyenberg Evaporated Goat Milk.

Meyenberg is nutritionally equivalent to evaporated cow's milk—economical, sterilized, and easy to prepare for feeding.



► Advertised to the profession only

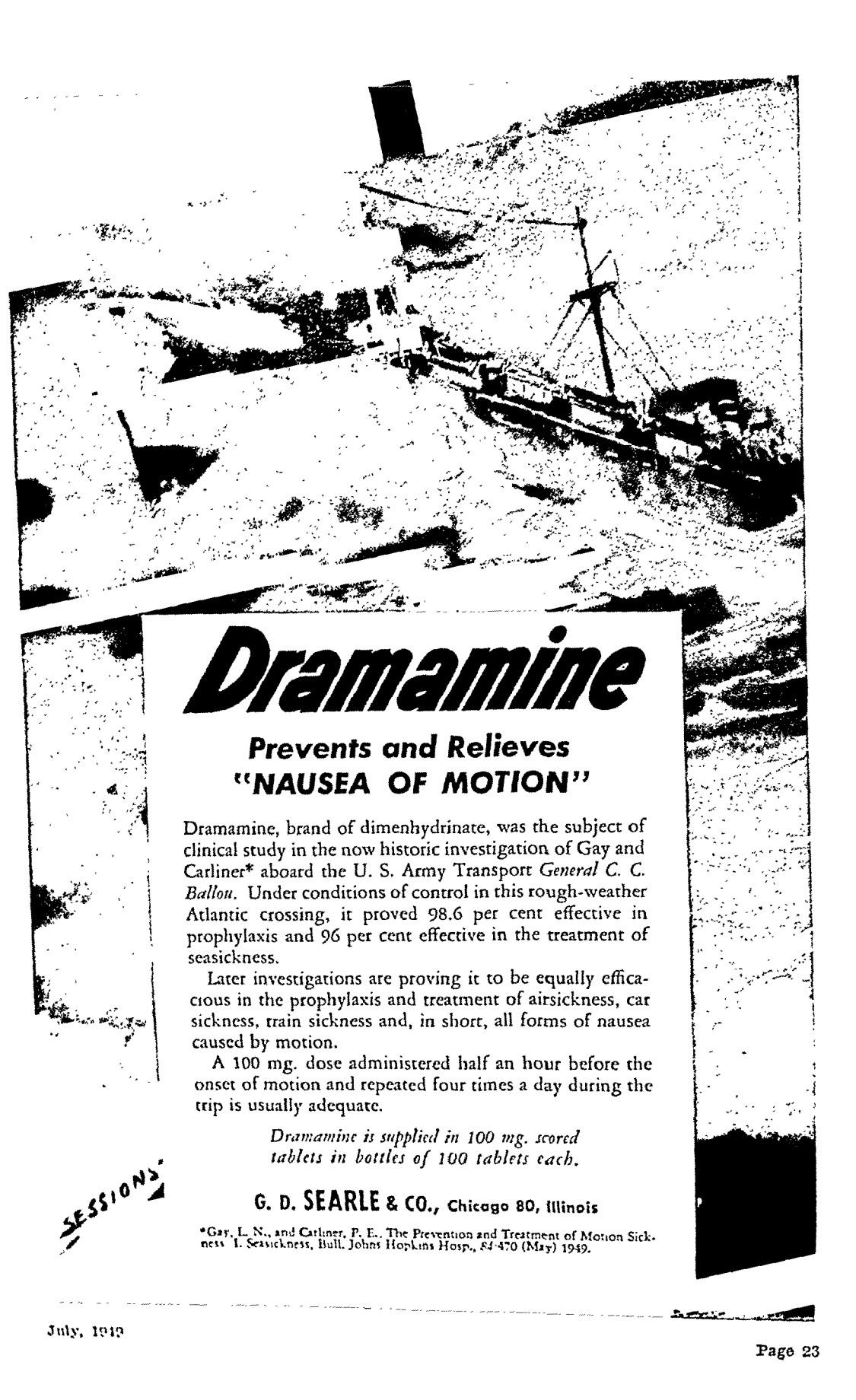
► Available at all pharmacies in 14 oz. hermetically-sealed containers

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SPECIAL MILK PRODUCTS INC.

LOS ANGELES 25, CALIFORNIA



Dramamine

Prevents and Relieves "NAUSEA OF MOTION"

Dramamine, brand of dimenhydrinate, was the subject of clinical study in the now historic investigation of Gay and Carliner* aboard the U. S. Army Transport *General C. C. Ballou*. Under conditions of control in this rough-weather Atlantic crossing, it proved 98.6 per cent effective in prophylaxis and 96 per cent effective in the treatment of seasickness.

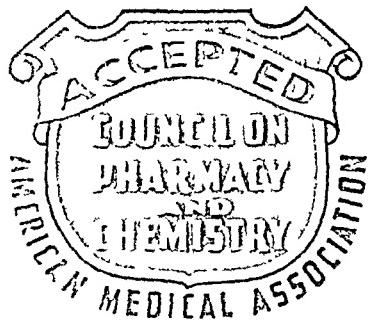
Later investigations are proving it to be equally efficacious in the prophylaxis and treatment of airsickness, car sickness, train sickness and, in short, all forms of nausea caused by motion.

A 100 mg. dose administered half an hour before the onset of motion and repeated four times a day during the trip is usually adequate.

Dramamine is supplied in 100 mg. scored tablets in bottles of 100 tablets each.

G. D. SEARLE & CO., Chicago 80, Illinois

*Gay, L. N., and Carliner, P. E. The Prevention and Treatment of Motion Sickness. I. Seasickness, Bull. Johns Hopkins Hosp., 84-470 (May) 1949.



NOW
ACCEPTED

SULFADIAZINE with SODIUM LACTATE—MRT



Each 5 cc. (one teaspoonful) provides:

0.5 Gm. Sulfadiazine
1.5 Gm. Sodium Lactate

in Palatable Liquid Suspension

Therapeutically Active • Minimum Renal Involvement • No "bicarb" Therapy Needed • Self-Alkalizing • Ideal for Infants as well as Adults • Palatable • Easily Administered Either Plain or Admixed.

SULFADIAZINE WITH SODIUM LACTATE—MRT—available in 16 fluid ounce and gallon containers at all prescription pharmacies.

SULFADIAZINE WITH SODIUM LACTATE—MRT—another original contribution of Marvin R. Thompson—is manufactured under U. S. Patent No. 2,460,437.

no coined names . . . specify



literature and samples on request

original contribution by MARVIN R. THOMPSON, INC.
STAMFORD, CONNECTICUT
Service to Medicine



When Rapid Growth Calls For HIGH IRON and THIAMINE

Instant Ralston and Hot Ralston Cereals are rich sources of iron and thiamine. Composed of whole-grain wheat with added wheat germ, thiamine and iron phosphate, the following percentages of the minimum daily requirements are supplied by —

	a SINGLE 1-ounce serving	IRON	THIAMINE
1-6 years		113%	84%
6-12 years		84.9%	56%
Over 12		84.9%	42%

Send for FREE Feeding Directions Forms:
birth to 3 mos., 3-6 mos., 6-10 mos., over 10 mos.

RALSTON PURINA COMPANY
JP-J Checkerboard Square, St. Louis 2, Mo.





*Conservative
Management*

WITH

BACITRACIN



REDUCES THE NEED FOR INCISION

In the management of carbuncle and a host of other local cutaneous infections the early use of bacitracin greatly reduces the need for incision and drainage in a vast majority of patients. Injected directly into the lesion, bacitracin (500 U./cc. in sterile isotonic sodium chloride solution) exerts a profound antibiotic influence upon the invading pyogens. Bacitracin is particularly effective in the presence of penicillin-resistant staphylococci and streptococci, and in mixed infections. Topical administration of bacitracin solution hastens resolution, minimizes pain, and in most cases averts the need for local surgery.

Bacitracin, topically administered, is a valuable means of treating a wide variety of local infectious processes. Physicians are invited to send for descriptive literature.

SUPPLY

Bacitracin-C.S.C. is supplied in 20 cc. size rubber-stoppered vials containing 2,000 and 10,000 units, and in 50 cc. rubber-stoppered vials containing 50,000 units.

C.S.C. Pharmaceuticals

A DIVISION OF COMMERCIAL SOLVENTS CORPORATION, 17 EAST 42ND STREET, NEW YORK 17, NEW YORK

directed therapy *for*
infectious infecções

THALAMYD

phthalylsulfacetimide-Schering

THALAMYD* has useful properties for combating sulfonamide-sensitive enteric organisms in bacillary dysentery, in ulcerative colitis, and in the preoperative sterilization of the intestine. Therapeutic dosage does not lead to detectable sulfonamide blood levels, hence there is no problem of systemic toxicity sometimes occurring with "absorbable" sulfonamides. Renal damage and aberrations of the blood picture do not occur. THALAMYD is absorbed, however, by diffusion, into the intestinal wall, where effective local concentration is established — where highest antibacterial action is required. Thus,



in preoperative sterilization, the bacterial flora can be virtually eliminated after four to five days treatment with THALAMYD. Thus elective intestinal surgery can be planned for this optimum time and carried out with minimal risk of infection;¹

in ulcerative colitis, there is both symptomatic and objective benefit in more than half of the cases, according to x-ray and sigmoidoscopic criteria.²

THALAMYD, Schering's phthalylsulfacetimide, tablets of 0.5 Gm., bottles of 100 and 1000 tablets.

1. Seneca, H., and Henderson, E.: In press.

2. Heineken, T., and Seneca, H.: Rev. Gastroenterol. 15:611, 1948.

*THALAMYD trade-mark of Schering Corporation



Schering CORPORATION • BLOOMFIELD, NEW JERSEY

Urinary pH No Problem *with*



MANDELAMINE

REG. U. S. PAT. OFF.

Urinary Antiseptic of Choice

MANDELAMINE* therapy is simple; it requires no complicated regimen involving adjuvant acidifying or alkalinizing agents to enhance efficacy or reduce toxicity.

Carroll and Allen,¹ reporting the results of a clinical study comprising 200 cases, write:

"The administration of Mandelamine maintained an acid urine without dietary restriction or other drug therapy, excepting in those cases in which urea-splitting organisms were present."

MANDELAMINE'S effectiveness in both acute and chronic cases of urinary infection and its remarkable freedom from toxic reactions further commend it as the urinary antiseptic of choice.

SUPPLIED: Enteric-coated tablets of 0.25 Gm. (3½ gr.) each, bottles of 120, 500, and 1,000.

1. Carroll, G., and Allen, N. H.: J. Urol. 55: 674 (1946).

*MANDELAMINE is the registered trademark of Nepera Chemical Co., Inc., for its brand of Hexydaline (methenamine mandelate).

NEPERA CHEMICAL CO., INC.
Manufacturing Chemists
NEPERA PARK • YONKERS 2, N.Y.

OUTSTANDING FEATURES

- 1 No gastric upset
- 2 No dietary or fluid regulation
- 3 No supplementary acidification (except when urea-splitting organisms occur)
- 4 Wide antibacterial range
- 5 No danger of drug-fastness
- 6 Simplicity of regimen—3 or 4 tablets, t.i.d.

Alhydrox*

Builds solid immunity step by step

Like Mr. McGinty's brick wall which stands solidly against the ravages of time because he builds it carefully, solidly, brick upon brick, the immunity you build with CUTTER "ALHYDROX" vaccine is solid.

*Cutter trade name for aluminum hydroxide adsorbed products

"Alhydrox" is a CUTTER exclusive—developed and used exclusively by CUTTER for its vaccines and toxoids. It supplements the physician's skill by producing these immunizing advantages:

1. "Alhydrox" adsorbed antigens are released slowly from tissue, giving the effect of small repeated doses
2. "Alhydrox", because of its more favorable pH, lessens pain on injection and reduces side reactions to a minimum
3. "Alhydrox" selectivity controls the absorption of antigens, reducing dosage volume while building a high antibody concentration. Reduced volume means less tissue distention and less pain

CUTTER LABORATORIES • BERKELEY 10, CALIF.

Specify "Alhydrox" when you order vaccines

AN EXCLUSIVE WITH...

CUTTER



Allergy	Total Cases	No Benefited	% Benefited	% Side Reactions
Hay Fever	562	387	68.8	11
Vasomotor Rhinitis	133	87	65.4	8
Asthma	189	82	43.3	6
Urticaria	48	39	81.2	11.5
Angioneurotic Edema	12	8	66.6	0
Contact Dermatitis	18	12	66.6	7.6
Atopic Eczema	17	14	82.3	40
Serum Sickness	3	3	100.0	0
Migraine	10	7	70.0	25
Allergic Headache	5	3	60.0	0
Drug Allergy	2	2	100.0	0
	999	644	64.5	10.9



Here's the Evidence

---based on clinical findings in 999 cases

- NEOHETRAMINE IS EFFECTIVE. It is useful in many patients in whom other antihistaminics produce marked sedation or other undesirable side-effects in the management of hay fever and other allergic disorders

- NEOHETRAMINE IS LESS TOXIC than other available antihistaminics, its lower toxicity is quantitatively more pronounced than its lower effectiveness

- Prescribe NEOHETRAMINE HYDROCHLORIDE, brand of Thonzylamine Hydrochloride

- Tablets .25 mg, .50 mg, 100 mg, Syrup—6.25 mg per cc—bottles of 1 pint and 1 gallon

- Neohetramine is the registered trademark of the Nepera Chemical Co. Inc. for its brand of Thonzylamine N,N dimethyl N,p methoxybenzyl N-(2 Pyrimidyl) ethylene diamine monohydrochloride



WYETH INCORPORATED
PHILADELPHIA 3, PA



Over 1,000,000
bouncing babies say:

"Thanks, Doctor,
for recommending
Swift's Meats for Babies!"

Of course, babies can't say thanks. But nonetheless, it's thanks to the good advice of their physicians that over a million infants today are thriving on Swift's Meats for Babies!

Specially prepared meats for babies—pioneered by Swift—offer an excellent source of biologically valuable proteins. They make available simultaneously all essential amino acids—for optimum protein synthesis. Low in fat content, Swift's Meats for Babies provide goodly amounts of natural B vitamins and food iron.

For earlier meat-feeding

Swift's Strained Meats are smooth and fine in texture. They may easily be bottle-fed in the early weeks of life.

For older babies and young children Swift prepares Diced Meats—juicy tender,

SWIFT



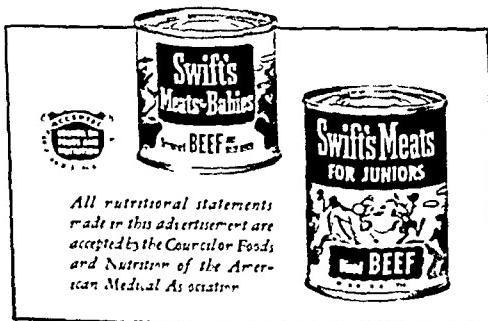
...foremost name in meats

...first to develop and clinically test 100% Meats for Babies

chopped to bite-size. These meats are firm enough to encourage chewing, flavorful enough to tempt "finicky" eaters. Six varieties: beef, lamb, pork, veal, liver and heart. Eating all six helps infants form nutritionally sound eating habits.

Swift's Meats for Babies are convenient, ready to serve!

Special note: In cases where infants are sensitive to milk proteins, Swift's Strained Meats may be tolerated very well. In such cases, many physicians recommend these meats be given in large quantities to replace milk proteins in the infant diet.



All nutritional statements made in this advertisement are accepted by the Council on Foods and Nutrition of the American Medical Association



WHEN THE DIET

Needs Supplementation

Comparison of the accompanying two columns of nutritional values readily shows why Ovaltine in milk has been so widely accepted as an effective multiple dietary food supplement in the feeding of children.

Column A lists the National Research Council's Recommended Daily Dietary Allowances for each 100 calorie portion in the diet of children of 4 to 6 years (42 lbs.). Column B lists the amounts of the same

*Based on average reported values for milk. Three servings of Ovaltine, each made of ½ oz. of Ovaltine and 8 fl. oz. of whole milk, the daily dosage recommended for diet supplementation, provide 676 calories.

nutrients provided by a 100 calorie portion of Ovaltine in milk.

	A N.R.C. Diet	B Ovaltine in Milk*
CALORIES.....	100	100
CALCIUM.....	63 mg.....	166 mg.
IRON.....	0.5 mg.....	1.8 mg.
PHOSPHORUS.....	63 mg.....	139 mg.
VITAMIN A.....	156 I.U.....	444 I.U.
THIAMINE.....	0.05 mg.....	0.17 mg.
RIBOFLAVIN.....	0.08 mg.....	0.30 mg.
NIACIN.....	0.5 mg.....	1.0 mg.
ASCORBIC ACID....	3.1 mg.....	4.4 mg.
VITAMIN D.....	25 I.U.....	62 I.U.
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Controlled Study CONFIRMS IMPORTANCE OF Morning Meal



A study* recently concluded at the Departments of Physiology and Nutrition of the college of medicine at a distinguished university established that the value of an adequate breakfast, as recommended by nutrition authorities, is definitely reflected in maximum work output and mental acuity during the pre-noon hour.

It also demonstrated that the long continued omission of breakfast detrimentally affects maximum work output, simple and choice

reaction time, and neuromuscular tremor.

Under adequately controlled conditions data were collected on the effects of four different breakfast habits on the maximum work output, mental acuity, and neuromuscular tremor of six young women ranging from 22 to 27 years in age. The breakfast habits investigated constituted habituation to an 800 calorie breakfast, effects of which were considered the critical standard, to no breakfast, to coffee only (1 cup of coffee, 1 ounce of cream, no sugar), and to a 400 calorie breakfast.

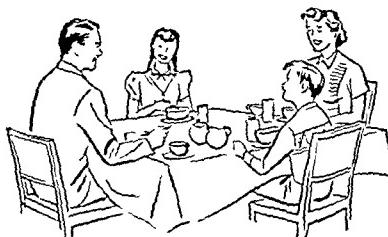
*Reprint of the study referred to
will be sent on request.

From the data gathered the following conclusions were reached:

1. When "no breakfast" was the morning habit, maximum work output showed a significant *decrease*, while a notable *increase* resulted in simple and choice reaction time and in tremor magnitude.
2. Habituation to coffee only showed a similar *decrease* in maximum work output, with corresponding *increase* in reaction time and in tremor magnitude.
3. When habituation to the 400 caloric breakfast was accomplished after the "coffee only" period, a significant *increase* over the findings in the "coffee only" period in maximum work output resulted and both simple and choice reaction time as well as muscle tremor magnitude showed a noteworthy *decrease*.

The authors point out that no direct comparison could be made of the physiologic responses during the 400 calorie and 800 calorie breakfast periods, because the breakfast period of "coffee only" occurred between the 800 calorie and 400 calorie periods.

This controlled investigation now provides experimentally established support for the widely advanced admonition "Eat an Adequate Breakfast." For, though the authors do not draw this conclusion, it may well be reasoned inversely that maximum work output should be increased, and mental acuity improved, when faulty breakfast habits are replaced by the eating of an adequate morning meal.



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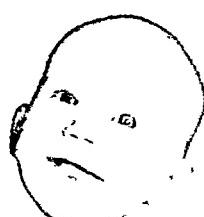
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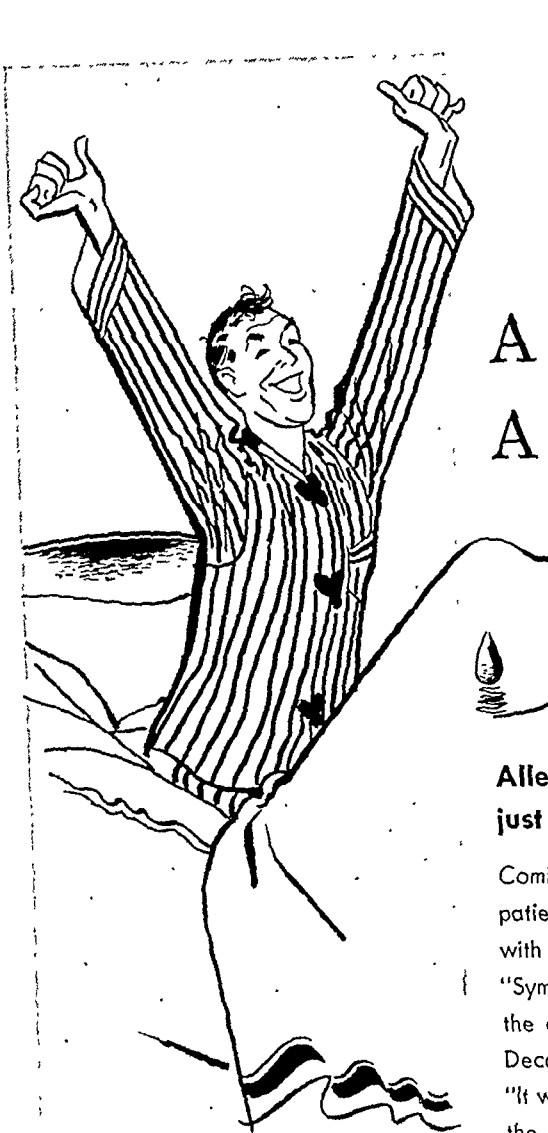
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1. Sheldon, J. M. et al: Univ. Mich. Hosp. Bull. 14:13-15 (1949). 2. MacQuiddy, E. L.: Neb. State M. J. 34:123 (1949).



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*Vital Statistics—Special Reports Vol. 25, No. 12, National Office of Vital Statistics, Washington, D. C. (Oct. 15) 1946, p. 206.



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*McLester, J. S.: Protein Comes Into Its Own, J.A.M.A. 139:897 (April 2) 1949.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.



American Meat Institute
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How Baby Lotion 10FA* reduces summer incidence of MILIARIA



As you know, during June, July and August, case incidence of miliaria soars, and with it, the case incidence of impetigo.

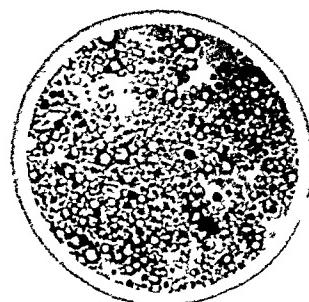
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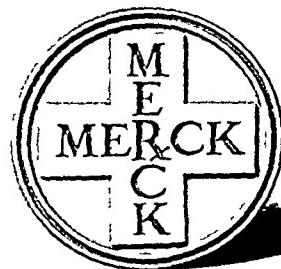
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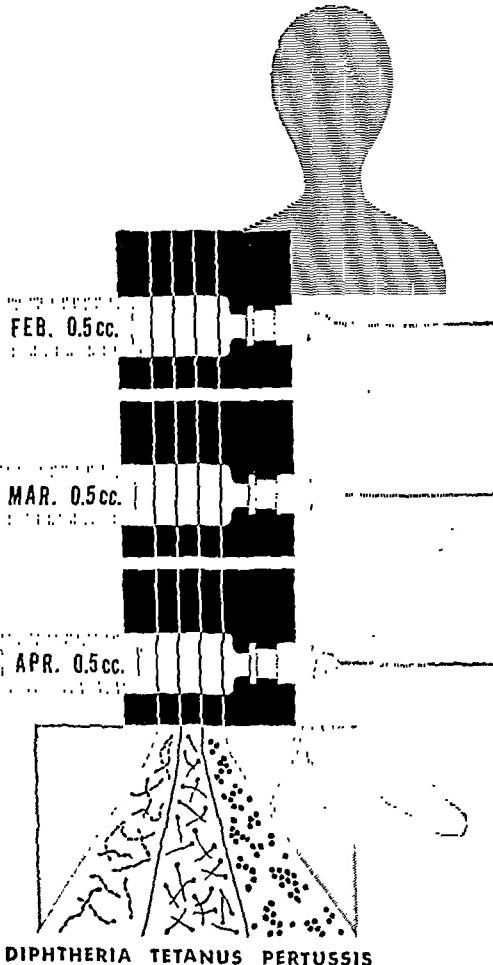
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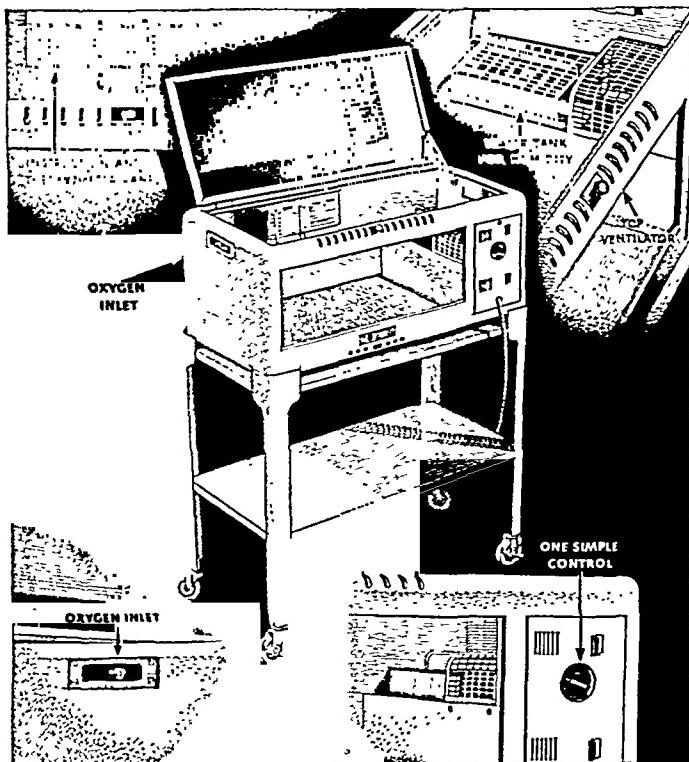
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Original Communications

THE CELIAC SYNDROME

FACTORS INFLUENCING ITS DEVELOPMENT WITH PARTICULAR REFERENCE
TO HYPOTHYROIDISM AS A CONTRIBUTING CAUSE

J. A. JOHNSTON, M.D., AND P. J. HOWARD, M.D.
DETROIT, MICH.

THE term *celiac syndrome* has been suggested to describe a group of digestive disturbances characterized by intolerance to fat or starch, either or both, with no implication of a uniform etiology. The excretion of bulky, foul stools, and enlarged abdomen, malnutrition, retarded growth, and evidence of deficiency of one or more vitamins and minerals are part of the picture. The classification suggested by Andersen and Hodges¹ is as follows: (1) "celiac disease," in which the primary defect is in the absorption of fatty acids from the intestine; (2) cases in which there is dietary intolerance of starch but not of fat; (3) congenital pancreatic insufficiency; (4) chronic mechanical obstruction of the pathways of digestion and absorption; and (5) cases presenting or suggesting the celiac syndrome but which do not fall into the above groups.

In a more recent contribution, Andersen² states her feeling that the presence of steatorrhea is not required for the first group, since it was only transiently present in treated patients. Nine of her patients who showed it on first examination failed to show it on a normal diet including whole milk a few weeks later. Increasingly, there is a tendency to attribute a number of the findings in these chronic digestive disturbances to deficiency states resulting from faulty absorption and not basically a part of the fundamental disturbance.

No single etiologic factor has been found in the celiac syndrome which explains satisfactorily its pathogenesis, except in the group of pancreatic fibrosis cases. Nasopharyngeal infection is said to be the commonest finding in the experience of Holt and McIntosh,³ and in twelve of our forty patients infection of the upper respiratory tract was prominent at the onset of the illness and during exacerbations. The frequency of this finding in children of the age group in which the syndrome is seen, and the rarity of the syndrome itself, call for a search for some other underlying conditioning factor which causes these children to react differently to such an infection than do otherwise normal children. A similar line of reasoning applies to the attributing of the symptoms to allergy:^{4, 5} there are undoubtedly instances in which the failure of absorption

From the Department of Pediatrics, Henry Ford Hospital.
Read before the American Pediatric Society in May, 1948.

seems referable to sensitivity, and yet a very small percentage of allergic individuals show the celiac syndrome. Five of our forty patients gave histories or findings suggesting allergy; though in none did it seem to be the entire explanation of the difficulty. None showed skin reactions to foods, though in two the introduction of an item found not to be tolerated would provoke abnormal stools. A third factor that we feel may well contribute to digestive difficulties, the psychogenic, is well accepted as a cause for a variety of gastrointestinal difficulties in older children and in adults, but seems not to have been considered seriously in this group. In the histories of eleven of our patients we were impressed by the possibilities of the role of insecurity, parental overanxiety, and frank mismanagement as contributing to the disturbance.

It has been our experience in a number of instances that the use of thyroid has been valuable in promoting a normal rate of growth when this has not been achieved by diet alone, and in some instances it has been valuable in shortening markedly the duration of the digestive symptoms also. Furthermore, there are a number of features in some cases of celiac disease which suggest hypothyroidism. It is the purpose of this paper to discuss thyroid deficiency as a factor contributing to the etiology of chronic intestinal indigestion.

A fourth factor always explored in the search for and explanation of a disturbance of growth is an endocrine one, and the following experiences are offered in support of the thesis that in a condition that may have multiple causes, thyroid deficiency is a conditioning factor in its development. Andersen's² recent hypothesis is that the condition is "believed to result from a deficiency of multiple nutritional factors complicating and resulting from a basic constitutional disease" and that "there is suggestive evidence that the difficulty in protein metabolism, shown by the high requirement for dietary protein and a tendency to hypoproteinemia on a normal diet, may be an expression of the basic disease." It is our thought that this "basic constitutional disease" may in some instances involve a thyroid deficiency on which is superimposed some other trigger mechanism such as infection, allergy, or emotion.

One of the outstanding findings in the condition is the disturbance of growth, and as we have watched the development of the condition in children whom we have followed from birth, we are impressed with the frequency with which a flattening of the curves of height and weight has preceded the abnormal stools. There has always been accepted as a part of the picture a retardation in the time of appearance of the centers of ossification, but this has been dismissed, somewhat gratuitously it seems to us, as a result of the fecal losses rather than as an integral part of the metabolic difficulty. In many of our cases it would appear that digestive symptoms have appeared later than would explain the retardation of bone age. Studies were done on thirty-two cases and showed delay in twenty-six, as judged by the standards of Vogt and Vickers³ from the Harvard Growth Study. We were impressed with Todd's⁴ statement that these have greater value when studied serially than

when attempt was made at a single assessment. Seventeen cases of pancreatic fibrosis are not considered here other than to point out that in seven of these in whom "bone age" was determined, in six it was found normal. If delay in the appearance of the centers of ossification were to be explained as a result of the digestive difficulty rather than an underlying cause, we should expect this group to show it in more extreme fashion than any. Osteoporosis was marked, but in only one was the appearance of centers delayed.

It seems to us significant that the commonest time of appearance of bowel symptoms, the latter half of the first year and the first half of the second (in twenty-three of our cases symptoms appeared between the seventh and eighteenth month of age), coincides with a decelerating phase and a falling rate of metabolism. It recalls a similar period in adolescence when the normal falling rate which follows the onset of puberty, physiologic though it be, carries with it a marked increase in the incidence of hypothyroidism. There is a normal tendency to recover from this fall; in Wetzel's⁸ calculations an accelerating phase appears at 3½ years. Topper and Mulier⁹ agree that the postpuberty fall likewise will be recovered from in the adolescent girl. The response of the anemia, the lassitude, the hypotension, low metabolism, and the menstrual irregularity to thyroid is so brilliant that to withhold this therapy would seem like poor judgment. Brailsford Robertson¹⁰ in particular stressed the vulnerability of the decelerating phase of growth noted in the latter part of the first year. Again, the infrequency with which it is seen in the first few months suggests the situation seen in the cretin, whose failure to show the effects of his deficiency in the first few months results from the influences of his mother's hormone. However in seven cases there was a history of pylorospasm or enterospasm in the first few months.

Hypothyroidism and the celiac syndrome have in common abnormalities in the metabolism of protein, fat, carbohydrate, and calcium, and in gastrointestinal motility.

The effect of thyroid on protein is covered in two studies from this clinic.^{11, 12} The high requirement for protein of which Andersen speaks is characteristic of the child with thyroid deficiency because this hormone is essential for the anabolic processes involving nitrogen in growth.

The flat oral tolerance curve noted in the celiacs, admittedly nonspecific and common to a number of conditions, is seen in the hypothyroid.¹³ Svensgaard¹⁴ reports a series of studies with the oral tolerance curve on subjects that included cretins and celiacs. Both showed flat curves, those of the cretin becoming erect with thyroid. She did not give thyroid to celiacs. An average of the data on four of her cretins before and after treatment with thyroid is shown in Table I.

TABLE I. AVERAGE OF SVENSGAARD'S DATA ON FOUR CRETINS

	FASTING SUGAR	MAXIMAL VALUE	DURATION OF HYPERGLYCEMIA
Before	74	133	110 minutes
After	79	229	125 minutes

That the defect in the utilization of glucose in celiac disease involves a failure of absorption is generally conceded.¹⁵ May and McCreary¹⁶ concluded that their low blood sugar curves seem to be "merely a reflection of the inactivity in gastro-intestinal motility" and confirmed the findings of similar curves in the cretin. A similar failure is shown in the thyroidectomized animal in whom Althausen¹⁷ shows a reduction in absorption of 50 per cent. This he attributes to a failure of the normal function of the thyroid in stimulating phosphorylation in the intestinal mucosa. Adequate replacement was shown to correct the deficiency rapidly and effectively.

Impaired fat absorption in the hypothyroid as measured by the vitamin A absorption test is of a degree comparable to that found in the celiac (Clausen and McCoard,¹⁸ May and McCreary¹⁹), but whereas in the celiac carotene is also reported low, the hypothyroid is said to have an abnormally high level, his defect involving a failure of conversion of carotene to vitamin A. It could be expected, however, that when a condition characterized by poor absorption and steatorrhea is superimposed on one in which a hormone defect results in poor conversion, the carotene level would not be helpful. When it was found high, it was not at a time when diarrhea was prominent. Using the single dose four- or five-hour test,²⁰ ten of our cases showed a level of vitamin A of less than 30 μg , seven from 31 to 50 μg , and six higher than 50 μg . Carotene was below 100 μg in twelve, between 100 and 200 μg in four, and in seven it was over 200 μg . There were two abnormally high figures of 410 μg and 510 μg . The last figure was obtained on a subject who had had an adequate celiac diet but had not yet had thyroid.

In these studies a factor of 7.38 was used for the conversion of our values on carotene recorded in micrograms to the "units" of May and McCreary and 2.05 for converting micrograms of vitamin A to their units. Accordingly, the normal standards would be as shown in Table II.*

TABLE II

AGE GROUP	CAROTENE		VITAMIN A	
	MAY UNITS	μG	MAY 620 UNITS	μG
4 days-5 mo.	3.1-7.5	22.0-55	7.1-13	14-26.6
9 mo.-2 yr.	34.8-72.4	256.0-534	13.1-19.9	26-40
3 yr.-5 yr.	36.4-75	268.0-553	10.1-19.2	20-39
6 yr.-10 yr.	19.4-59	143.0-435	8.1-21.5	16-44
11 yr.-12 yr.	10.5-56	77.4-413	9.4-20.9	19-42

Rickets and tetany have both been seen in celiac disease and the failure to absorb calcium normally has been noted in balance observations.^{21, 22} It was the negative calcium balance of the cretin made positive by thyroid that led us to use it in treating the obstinate tetany in the case of J. M. In a previous study,²³ we had shown that normal retentions of calcium could be expected only with a normal level of thyroid activity and that the cretin failed to store until he received thyroid, his losses being referable to large fecal excretions, the hyperthyroid's negative balances being the result of excessive losses both through the urine and the stool.

*For these calculations we are indebted to Dr. George H. Mangun.

Impairment of tone and sluggish peristalsis, held responsible for the clumping noted in celiac disease, are found in hypothyroidism, though Hamilton and associates²⁴ also demonstrated hypermotility of the stomach in adult hypothyroids becoming normal under treatment with thyroid.

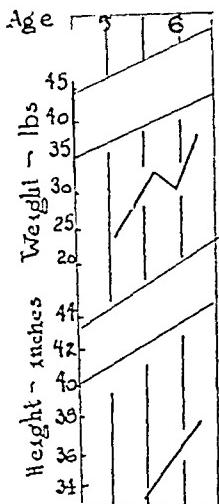
Thus a number of the findings seen in the one condition are duplicated in the other, save the abnormal stools. It is our thought that a certain percentage of infants have their digestive disorder precipitated by infection, emotion, and allergy, but that its development is conditioned by an underlying thyroid deficiency and that the complementing of the high protein diet with thyroid would notably shorten the duration of the mild case and in the severe case would correct an otherwise irreplaceable deficit.

The question will arise as to the confusion of a true primary hypothyroid state with the "hypometabolism" seen as a result, for example, of a low protein intake²⁵ or prolonged inactivity. In a study of two children¹¹ whose metabolic rate had fallen as a result of a year's inactivity, we showed that small amounts of thyroid were anabolic, as judged by the fact that they produced increased storage of nitrogen and calcium. Larger amounts became katabolic unless the intake were increased. It was possible to achieve an increased intake, however, only when the metabolic rate had been elevated with thyroid. The mechanism of the lowered rate of oxidation may be quite different in the two conditions, but there would seem to be the same usefulness in thyroid as a therapeutic agent, provided the dose is kept small.

The first experience leading to this thought was the demonstration of the effectiveness of thyroid in the correction of a failure to absorb calcium normally in two conventionally treated celiacs.

CASE 1.—T. M.,^{*} a male child, was seen at 5 years of age with a history of onset of bowel disturbance at 1½ years. Abdominal enlargement and failure to gain had been noted for three years, and, although a high protein diet had been followed by a reduction in the number of stools from ten to two, the stools had continued to be large and frothy. The family history showed that one sibling has celiac disease and one a history suggestive of it. During the patient's first year his feeding history had not been unusual. He was breast-fed for three months, followed by lactie acid milk with Karo formula; cod liver oil was later replaced by 10 drops of viosterol; orange juice had been given since 3 months of age, cereal from 5 months, vegetables from 6, and eggs and meat after one year. Infection played no prominent role until the age of 3 years, when he had chicken pox, followed by pertussis at 4 and measles at 5 years. Stools showed a fat varying from 37 per cent to 63 per cent. Glucose tolerance (oral) was 55 mg., 50 mg., 61.5 mg., and 60 mg. at ½, 1, 2, and 3 hours. Intravenous pyelograms showed a double kidney pelvis, good excretion of the dye, and no dilatation of the pelves. Wrist plates showed a delay in ossification of at least two years. X-rays of the chest were negative. Blood calcium was 12.4 and phosphorus 3.0 mg. per cent. Blood showed 11.8 Gm. hemoglobin; white blood cells 3,800 with 64 per cent polymorphonuclears. Urine was negative. Barium meal showed the "clumping and segmentation noted in vitamin deficiency and celiac disease." Treated in another hospital from July, 1938, to August, 1938, he was discharged to a convalescent home until November, 1938, and to his home

*For the care of T. M. we are indebted to Dr. James Wilson, Ann Arbor,



	Nitrogen	Calcium	Phosphorus
Control	11.46	11.55	15.50
Thyroid	15.68	16.40	16.56
Urine	7.71	8.33	0.040
Stool	1.39	1.46	15.30
Balance	2.36	1.76	-0.020
		0.126	0.355
			0.280

A



B.



C.

Fig. 1.—T. McP., 6 years of age. It had been possible to control the character of this boy's stools reasonably well with the cellulose diet, but growth was unsatisfactory and he was subject to frequent relapses. Bone age was grossly delayed. A, Chart. B, X-ray at 5 years, 4 months of age. C, X-ray at 9 years, 4 months of age.

Note: In A, and the following charts the silhouettes were traced directly from the x-ray films. In all of these weight charts the "normal zone" represents the sixteenth and eighty-fourth percentiles of the Iowa standards.

after that. He was readmitted in March, 1939, with a history again of large, gray, foul stools. These improved in the hospital, though they remained quite large. Data on his growth are given in Table III.

TABLE III. DATA ON GROWTH OF T. M.

DATE	AGE	HEIGHT (INCHES)	WEIGHT (LB.)
July, 1938	5 yr., 4 mo.	33½	23
November, 1938	5 yr., 8 mo.		32½
March, 1939	6 yr.	37	29
April, 1939	6 yr., 1 mo.	37	30
			Thyroid begun May 7, 1939
June, 1939	6 yr., 3 mo.	38	37

Balance studies for thirty-six days (significant figures for calcium require between fifteen and twenty days when the intake is not restricted) showed a negative balance for calcium entirely referable to fecal excretion, becoming positive with one grain of Burroughs-Wellcome thyroid for nine days and then two grains for eighteen days, which resulted in a rise in basal calories from 763 to 887 per twenty-four hours. Interpretation of the "basal rate" is confused by the child's dwarfism; by the Boothby surface area standards these determinations would be minus 7 and plus 18, respectively.

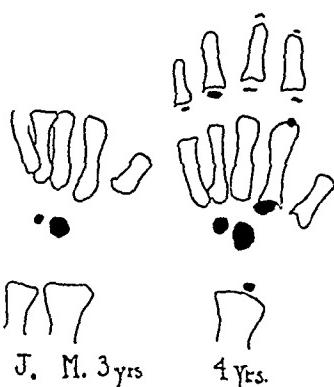
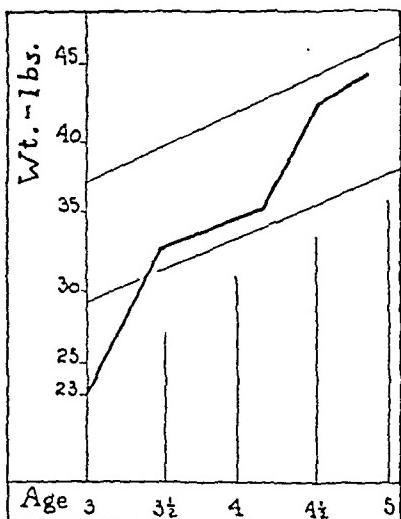
A negative calcium balance of 20 mg. per day was converted with thyroid to a positive balance of 126 mg. per day. Phosphorus and nitrogen retention fell slightly (Macy's²⁶ normal mean retention of calcium at 5 years was 172 mg. per day).

TABLE IV. T. M.

NITROGEN (GM. PER DAY)		CALCIUM (GM. PER DAY)		PHOSPHORUS (GM. PER DAY)		BASAL CALORIES IN (24 HR.)		B.M.R. (BOOTHBY)		
CONTROL	THYROID	CONTROL	THYROID	CONTROL	THYROID	CONTROL	THYROID	CONTROL	THYROID	
Intake	11.46	11.55	1.550	1.568	1.640	1.656	763	887	-7	+18
Urine	7.71	8.38	0.040	0.031	0.559	0.721	--	--	--	--
Stool	1.39	1.46	1.530	1.411	0.726	0.715	--	--	--	--
Balance	2.36	1.76	-0.020	+0.126	0.355	0.280	--	--	--	--

CASE 2.—J. M.,* a male child born weighing 5 pounds apparently at term, did well nutritionally the first year on a diet of evaporated milk, water and Dextri-Maltose, orange juice, cod-liver oil, cereal, vegetables, and meat. History was uneventful until the age of 2½ years; he stood at 10 months but did not walk until 18 months of age. From 2½ to 3 years of age, he lost weight, the abdomen became distended, and the stools, at first yellow and watery, became large, foul, and frothy. Two months before admission the hands were noted to be held in spasm and there was some stiffening of the body. At this time, aged 3 years, he appeared severely malnourished, with little subcutaneous fat, shrunken buttocks, and a large abdomen. His measurements were as follows: length, 37 inches; weight, 23 pounds; head, 18½ inches; and chest, 18 inches. He was showing definite tetany. The blood calcium was 7.3, phosphorus 2.1, phosphatase 0.8 units. The glucose tolerance curve was flat. He was treated for six weeks with calcium chloride, viosterol, and a celiac diet. He was referred to this clinic for balance studies, and at admission, aged 3 years, 3 months, the blood calcium was 5.0 mg. per cent, phosphorus 2.84 mg., and phosphatase 2.72 units. The wrist showed two

*For the case of J. M. we are indebted to Dr. Clement A. Smith, Boston.



Control Thyroid
18-day 18-day
Calcium Nitrogen Calcium Nitrogen

Intake	953	15.60	836	14.36
Urine	87	8.52	47	7.36
Stool	812	1.48	496	1.53
Balance	54	5.60	293	5.47
%	5		35	

A.



B.

Fig. 2.—J. M.'s condition was complicated by recurrent tetany. Thyroid resulted in increasing his retention of calcium from 5 per cent of the intake to 35 per cent. A, Chart. B, X-ray at 3 years of age.

carpal centers at 3 years of age. Serum albumin was 3.18 and globulin 1.64. A balance study was conducted for thirty-six days, during the latter eighteen of which he received thyroid. The intake was derived from items in the celiac diet and was analyzed in duplicate for nitrogen and calcium.

TABLE V

	18-DAY CONTROL		THYROID $\frac{1}{4}$ GRAIN PER DAY.		18 DAYS
	CALCIUM	NITROGEN	CALCIUM	NITROGEN	
Intake	953 mg.	15.6 gm.	836 mg.	14.36 gm.	
Urine	87	8.52	47	7.36	
Stool	812	1.48	496	1.53	
Balance	54	5.60	293	5.47	

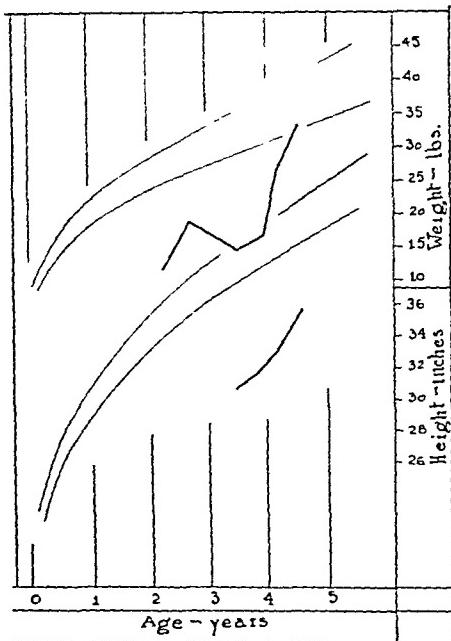
Seven months later he returned with the history of doing well until three months previous, when the stools became abnormal and he lost weight. At this time an intensive course of vitamin B parenterally was given following May's suggestion without measurable effect. Home cooperation on diet and medication was completely untrustworthy and he had several setbacks which the mother explained by the dropping of both thyroid and the diet and increasing of the starch intake. A 3-year-old plate showed marked osteoporosis and only two carpal centers. At 4 years the wrists showed only two centers on either side, with the radial head on one side. At 4½ years he had a recurrence of tetany. At this time his prothrombin was found to be 20 per cent of normal. At 5 and 5½ years there were recurrences of tetany, the blood on the last admission showing calcium of 7.4, phosphorus 6.3, and phosphatase of 3.2.

It could be concluded from this case that hypocalcemic tetany was correctable by replacement therapy with thyroid. Diet alone had been tried for three months. Thyroid was dropped for considerable periods before each of these readmissions.

CASE 3.—Ru. B., a female child, was seen at 6 years for dwarfism and failure to develop mentally; celiac stools were observed only intermittently. She was first studied in another institution at 2 years of age, unable to stand and weighing 13 lb. Stools were large but formed, save on occasions when they became loose and foul. She showed a marked retardation of bone age, a flat oral glucose tolerance curve, normal calcium and phosphorus, a phosphatase of 2 units, and cholesterol of 201. During the next two years she gained well while on a high protein, high vitamin diet but she entered the hospital four times, each time with a sharp loss of weight. At 4 years of age she weighed 15 lb. and was 30¾ inches in height. Her recovery after the diet was supplemented by thyroid was started as measured by height, weight, and bone development is recorded on the chart, but is not nearly so dramatic as her mental progress. The history of her twin, obtained from another institution, follows.

CASE 4.—Ro. B.^a, a premature male twin of Ru. B., was hospitalized because of the complaint of slow mental development and dwarfism. He was 2 years old, weighed 11 pounds, 15 ounces, and was 26½ inches in height. The five other children were normal, as were the parents. He sat up at the age of 2 years. He did not appear ill, but was inactive. With a good diet the child gained one pound in seven days and seemed improved. During the following five months the child failed to improve at home, and was readmitted at the age of 2 years, 9 months, weighing 11 pounds, 9 ounces. He still did not talk, walk or stand alone. At this time bowel movements were stated to be large

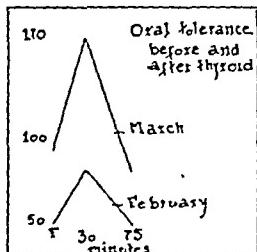
*For the care of Ro. B. we are indebted to Dr. Paul V. Woolley, Detroit.



27¹⁵



4 years



Basic phosphatase

2/47 . . . 287
12/47 . . . 468

A.



B.



C.

Fig. 3.—Ru. B. She was treated sporadically as a celiac for four years. No growth occurred until thyroid was started, although her stools could be controlled by a celiac diet. Her twin died with an identical history shortly before thyroid deficiency was appreciated in Ru. A. Chart. B, X-ray at 2 years, 9 months of age. C, X-ray at 7 years of age.

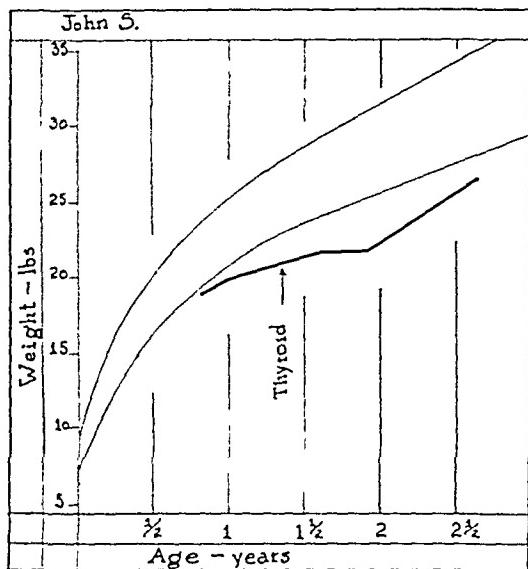
and foul. The x-rays of the long bones showed irregularity of the diaphyseal ends and patches of periostitis. The blood phosphorus was 5.5 mg. per cent, and phosphatase 0.9 Bodansky units. The blood cholesterol was 349 mg. per cent. The oral dextrose tolerance curve was 83, 90, 72, 75, and 67 mg. per 100 c.c. at fasting and 30, 60, 120, 180 minutes. He was placed in a convalescent home, and under careful feeding his weight increased to 24 pounds, 12 ounces, and he was sent home to convalesce further. Again under home care the child progressively failed and died. This child would, in retrospect, appear to have duplicated his sister's course and to have had as great a need for thyroid as she.

CASE 5.—R. K., a male child, was born at term of a mother said to have thyroid deficiency and arthritis. Birth weight was 8 pounds. Growth and development were fairly normal for a year; he walked at 13 months of age, and said several words at 17 months. From age one to 2 years he had grossly abnormal stools, six to ten a day, fermentative and greasy, and the abdomen became distended. He improved on a high protein diet. One hand became swollen at 2 years, one foot at 4 years of age. At about this time he appeared edematous, with frank puffiness of the eyes, and he was referred for study with a question of nephrosis, although studies in another hospital had shown a normal urine but a very low serum protein. At 4½ years the weight was 39 pounds, the height 39 inches. He appeared pale and puffy. There was frank swelling of the phalangeal joints of the right hand and the left ankle. Wrist studies showed only two carpal centers. Thyroid was begun and improvement was marked. The following observations were made eight months later: cholesterol 143; phosphatase 5.7 units; vitamin A absorption 13.8 µg per cent; carotene 54.2 µg per cent. Allergy tests showed reaction to alternaria, dust, and several bacterial proteins. Albumin was 2.05, globulin 1.46. Urine was negative. Cephalin cholesterol was negative. Stool fat was 19.3 per cent dry weight. An intercurrent respiratory infection in March, 1948, was followed by a recurrence of celiaclike stools and a loss of 3 pounds of weight.

TABLE VI

AGE	HEIGHT (INCHES)	WEIGHT (LB.)
Birth		8
4 yr., 4 mo.	39	39 (thyroid begun)
5 yr., 6 mo.	41	40

CASE 6.—The case of J. S. is offered as an example of the occurrence of the intestinal difficulty in a child in whom hypothyroidism had been suggested clinically four months before the stools became abnormal. Born normally and fed on an evaporated milk formula with added cereal and vegetables, his history was uneventful for fourteen months. A general check when he was 10 months of age occasioned the remark that he seemed an unusually placid baby and was not trying to pull himself erect. At that time he weighed 19 pounds, and the height was 28½ inches. At 14 months he returned with the complaint of five or six stools a day, marked irritability, and a flattening of the weight curve. The oral tolerance was 72, 76, 74, 54 mg. per 100 c.c. Vitamin A absorption was 31.0 µg and 180 µg carotene. Red blood count was 3,800,000; hemoglobin 10.9 Gm. Stool fat was 11 per cent dry weight. Wrist plate showed a single carpal bone at 16 months. Thyroid, grain ¼, was started, with a high protein diet; he was symptom-free in two months. On January, 1948, his height was 36 inches and weight, 27 pounds. The bone age in this case was sufficiently delayed to warrant the assumption that a re-



15 mos.
15 mos.



RBC 3.8 m. Hb_g 10.9 gm.
Glucose 10.1 - 72 76 74 51 mg/100cc
A absorption 31.9 mcg.
Carotene 180 mcg.

35 mo.

A.



B.



C.

Fig. 4.—J. S.'s history suggested thyroid deficiency at 10 months of age; celiac symptoms appeared at 14 months of age. A, Chart. B, X-ray at 15 months of age. C, X-ray at 35 months of age.

tarding influence antedated the gastrointestinal symptoms. In addition, there were clinical signs of hypothyroidism, lethargy, and slowness in development at 10 months of age.

The role of infection of the lymphoid ring in activating the process might be understood again as an item fulfilling Andersen's² postulate. In a previous study,²⁷ from which we reproduce one chart, it was shown that tonsillar infection, even without fever, exerted a striking catabolic effect on protein metabolism and that the removal of infected tonsils and adenoids was followed promptly by an improved retention of nitrogen. These children, however, had elevated metabolic rates which fell after the operation. Infection was present in eighteen of the forty cases and in twelve it seemed to play a dominant role, but in ten of the eighteen cases we had no evidence of thyroid deficiency. In

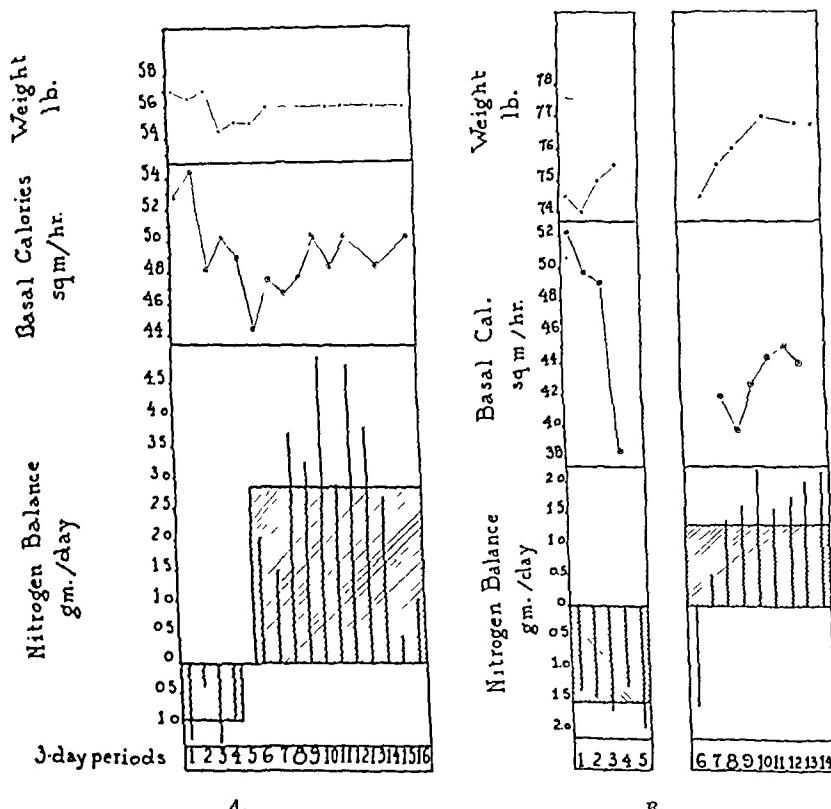


Fig. 5.—Chart showing the effect on the nitrogen balance of the removal of infected tonsils and adenoids. (From Johnston, J. A., and Maroney, J. W.: Focal Infection and Metabolism, *J. Pediat.* 12: 563, 1938.)

A, F. S., a boy 9 years old, height 50 inches, estimated weight, 58 pounds. Tonsillectomy was performed on the first day, fifth period. Nitrogen balance and basal metabolism were determined before and after removal of tonsils and adenoids. In this and subsequent charts the balances are continuous; each bar represents a three-day balance, and the average of all balances before and after is indicated by crosshatching.

B, S. R., a boy 12 years old, height 56 inches and estimated weight 78 pounds. Tonsillectomy was on the first day, sixth period. Nitrogen balance and basal metabolism were constant. Each bar represents a three-day balance and the average of all periods before and after tonsillectomy is shown by crosshatching.

eight we felt we had. In twelve of the forty cases infection of the tonsils and adenoids, or the adenoids alone, seemed to have etiologic significance. In one (Case No. 12), our concern with it probably led to our overlooking the possibility of its being superimposed on a thyroid deficiency, and a bone plate was not taken until the age of $4\frac{1}{2}$ years, when only two centers were found in the wrist and thyroid was started. Nevertheless, we feel that in some instances chronic infection of the adenoids and tonsils alone may constitute both the underlying metabolic flaw and the conditioning factor, and the usefulness of the procedure of tonsillectomy and adenoideectomy should be borne in mind constantly.

It would be well to stress again the fact that if thyroid is used, its anabolic effect will not be noted unless an increase in the intake of protein can be effected. In our original studies on the cretin, the increased storage was largely referable to an increase in intake. Recently in a juvenile myxedema no such increased storage occurred when we restricted the intake to the amount taken when the metabolism was at its lowest.

In this series we were further impressed with the probable role played by emotional factors in the etiology of the disturbed bowel function. Over-anxiety on the part of parents, engendering fears in early infancy, the lack of affection and of normal handling attendant or prolonged institutional stays in the case of two illegitimate children, and the insecurity in several instances related to the instability of army camp life, all must have left their marks, and several instances are summarized out of the eleven cases in which we felt that emotional disturbances made an etiologic contribution to the digestive disturbance.

It would be desirable to have some more quantitative assessment of the hypometabolic state than the bone age. The weakness of cholesterol is widely accepted, unless it be determined before, during, and after the administration of thyroid. The response of the growth curve is highly suggestive. We have felt that the suggestion of Talbot and associates,²⁵ who found the basic phosphatase consistently below 4 units in the cretin, and of Hill and Webber,²⁶ whose low metabolism determinations and clinical evidences of hypothyroidism were accompanied by low phosphatase, was highly useful and we include in Table VII, through the courtesy of Dr. Sidney Farber, figures (in addition to those quoted in the protocols) on three cases from the Children's Hospital of Boston. In two of these cases the bone was one-half the chronological age.

TABLE VII

CALCIUM	PHOSPHORUS	PHOSPHATASE
7.8 mg.	4.7 mg.	3.5 units
7.7	6.4	3.6
7.0	4.4	2.3

However, in a controlled series of our own we have found, in a group of orphans from poor homes, phosphatase levels below 4 when there was no other evidence of hypothyroidism. We feel, however, that the demonstration

of improved calcium absorption in the two cases in whom balance determinations were reported, the acceleration of growth, and the shortening of the average time duration of symptoms, are all adequate reasons for considering that in a certain percentage of cases the hypometabolic state of the infant with celiac syndrome is improved with thyroid medication.

The addition of thyroid to the other items in the management of this condition has seemed notably to shorten the duration of symptoms, in eighteen cases the average being nine months, in contrast to seventeen in those treated with diet alone, and five children were symptom-free in less than two months. A number of patients whose thyroid therapy was not instituted until after several years of symptoms are not included. In a condition complicated by the development of deficiency states, it is not suggested that there be any departure from the practice of utilizing the high protein, high vitamin diet.

SUMMARY

In summary, we suggest that chronic intestinal indigestion may be precipitated by a number of factors, infectious, emotional, allergic, but, that since all of those suggested do not commonly produce the disorder in otherwise normal children, Andersen's⁴ assumption of an underlying constitutional defect seems valid, and that in some instances this defect is a thyroid deficiency, while in others it is in the nature of a secondary hypothyroidism resulting from nitrogen and caloric deficits, in which case thyroid in small doses is indicated for its anabolic effect.

We do not feel that thyroid deficiency explains all cases but that a number will be found in whom the defect will be referable to other mechanisms relating to protein synthesis. The role of the liver in these cases warrants further study.

Dr. Frank Hartman supervised the metabolism determinations.

Dr. Oliver H. Gaehler supervised the balance determinations.

REFERENCES

1. Andersen, D. H., and Hedges, R. G.: The Celiac Syndrome, Brennemann's Practice of Pediatrics I, Hagerstown, W. F. Prior Company, Inc., p. 29.
2. Andersen, D. H.: Celiac Syndrome: Relationship of Celiac Disease, Starch Intolerance, and Steatorrhea, *J. PEDIAT.* 30: 564, 1947.
3. Holt, L. E., and McIntosh, R.: Holt's Diseases of Infancy and Childhood, ed. 11, New York, 1940, D. Appleton-Century Co., p. 274.
4. Kunstdater, R. H.: Gastrointestinal Allergy and Celiac Syndrome, *J. PEDIAT.* 21: 193, 1942.
5. McKhann, C. F., Spector, S., and Meserve, E. R.: Association of Gastro-Intestinal Allergy with Celiac Syndrome, *J. PEDIAT.* 22: 362, 1943.
6. Vogt, E. C., and Vickers, V. S.: Osseous Growth and Development, *Radiology* 31: 441, 1938.
7. Todd, T. Wingate: Atlas of Skeletal Maturation, St. Louis, The C. V. Mosby Company, p. 17.
8. Wetzel, N. C.: On the Motion of Growth; XVI.: Clinical Aspects of Human Growth with Special Reference to Infancy and Pre-school Life, *J. PEDIAT.* 4: 465, 1934.
9. Topper, A., and Mujlier, J.: Basal Metabolism of Normal Children: Puberty Reaction, *Am. J. Dis. Child.* 43: 327, 1932.
10. Robertson, T. B.: The Chemical Basis of Growth and Senescence, Philadelphia, 1923, J. B. Lippincott Co.

11. Johnston, J. A.: Factors Affecting Retention of Nitrogen and Calcium in Period of Growth; II. Effect of Thyroid on Nitrogen Retention, *Am. J. Dis. Child.* 58: 963, 1939.
12. Johnston, J. A.: Factors Influencing Retention of Nitrogen and Calcium in Period of Growth; V. Further Evidence of the Anabolic Effect of Thyroid on Calcium Metabolism, *Am. J. Dis. Child.* 62: 1172, 1941.
13. Janney, N. W., and Isaacson, V.: I. Blood Sugar in Endocrine Diseases, *Arch. Int. Med.* 22: 160, 1924.
14. Svensgaard, E.: The Blood Sugar in the Sick Child, *Acta. Pediat.* 12: Supp. 16, p. 83, 1931.
15. Crawford, T.: Causation of Low Blood Sugar Curve in Celiac Disease, *Quart. J. Med.* 8: 251, 1939.
16. May, C. D., and McCready, J. F.: Glucose Tolerance Test in Celiac Disease, Significance of Low Blood Sugar Curves, *J. PEDIAT.* 17: 143, 1940.
17. Althausen, T. L., and Stockholm, M.: Influence of Thyroid Gland on Absorption in Digestive Tract, *Am. J. Physiol.* 123: 577, 1938.
18. Clausen, S. W., and McCoord, A. B.: The Carotinoids and Vitamin A of the Blood, *J. PEDIAT.* 13: 636, 1938.
19. May, Charles D., and McCready, J. F.: The Absorption of Vitamin A in Celiac Disease, *J. PEDIAT.* 18: 200, 1941.
20. Pratt, L. L., and Fahey, D. R.: Clinical Adequacy of Single Measurement of Vitamin A Absorption, *Am. J. Dis. Child.* 68: 83, 1944.
21. McCrudden, T. H., and Tales, H. L.: Complete Balance Studies of Nitrogen, Sulphur, Phosphorus, Calcium, and Magnesium in Intestinal Infantilism, *J. Exper. Med.* 15: 450, 1912.
22. Bennett, T. I., Hunter, D., and Vaughn, J. M.: Idiopathic Steatorrhoea (Gee's Disease) a Nutritional Disturbance Associated with Tetany, Osteomalacia, and Anaemia, *Quart. J. Med.* 1: 603, 1932.
23. Johnston, J. A., and Maroney, J. W.: Factors Affecting Retention of Nitrogen and Calcium in Period of Growth; II. Effect of Thyroid on Calcium Retention, *Am. J. Dis. Child.* 58: 1186, 1939.
24. Hamilton, F. E., MacQuigg, R. E., and Curtis, G. M.: Hypothyroidism, The Gastric Motility in Certain Patients with Thyroid Deficiency, *J. Clin. Endocrinol.* 1: 24, 1941.
25. Johnston, J. A., and Maroney, J. W.: Relationship of Basal Metabolism to Dietary Intake, *Am. J. Dis. Child.* 51: 2039, 1936.
26. Maez, I. G.: Nutrition and Chemical Growth in Childhood, Vol. I, p. 161. Baltimore, 1942. C. G. Thomas.
27. Johnston, J. A., and Maroney, J. W.: Focal Infection and Metabolism: The Effect of the Removal of Tonsils and Adenoids on the Nitrogen Balance and the Basal Metabolism, *J. PEDIAT.* 12: 563, 1938.
28. Talbot, N. B., Hoessl, G., and Tuohy, E. L.: Serum Phosphatase as Aid in Diagnosis of Cretinism and Juvenile Hypothyroidism, *Am. J. Dis. Child.* 62: 273, 1941.
29. Hill, H. M., and Webber, J. E.: Serum Phosphatase Values in Children Showing Retardation in Osseous Development and Low Metabolic Rates, *J. PEDIAT.* 22: 325, 1943.

THE RELATION OF ILLNESS PATTERNS IN CHILDREN TO ORDINAL POSITION IN THE FAMILY

ALICE KINGSLEY, A.B., AND EARLE L. REYNOLDS, PH.D.
YELLOW SPRINGS, OHIO

THE long-term program of the Fels Research Institute includes serial medical examinations and interim health histories on approximately 300 children, who are being followed from prenatal life to maturity.¹ The present paper will be concerned with the illness records of 101 Fels children, forty-nine boys and fifty-two girls, during their first five postnatal years.

An attempt will be made to determine the extent to which a child's ordinal position in the family may be significantly associated with the type, incidence, and severity of certain disorders which he exhibits. The particular approach will be the study of various illness differentials as shown by singletons, first children, and second children.

Data on illness history are available from three sources:

1. A *medical examination*, given every third month during the first year, and every six months thereafter.

2. An *interval history*, a questionnaire mailed to all mothers at thirty-one intervals during the first five years: ten times during the first year, seven times during the second, six times during the third, and four times yearly thereafter. Information specifically requested includes details as to the duration and severity of illness, information on intestinal and urinary function, and problems of feeding. In the present study, 2,721 individual interval histories were evaluated.

3. An *illness history*, compiled by the Fels nurse, after conferences with the mother, during which the information sent in on the interval history is verified and complemented.

In the tabulation of illnesses, the following criteria were used:

Respiratory infections included colds, coughs, influenza, rhinitis, laryngitis, croup, pharyngitis, bronchitis, and pneumonia.

Tonsillitis was tabulated only when it was reported independently, not as a minor symptom accompanying a cold.

Vomiting included forcible expulsion, but not mild spitting up by infants under 9 months of age, nor vomiting with whooping cough.

Gastrointestinal disorders included such miscellaneous items as colic, nervous indigestion, bowel infection and intestinal influenza. If specific symptoms such as vomiting or diarrhea were reported, tabulation was made in those categories rather than here.

Skin disorders included urticaria, eczema, miliaria rubra, impetigo, poison ivy, and boils.

Accidents included dog bites, burns, bruises, cuts, fractures, and concussions.

Feeding disorders: One "attack" was tabulated for each interval history which reported any anorexia or refusal to eat. Dislike or refusal of a few particular foods was not tabulated, nor was anorexia which occurred during an illness.

Mild: appetite reported as occasionally fair or fickle.

Severe: appetite reported as poor at recurrent intervals or frequently; any forced feeding.

Constipation was tabulated in the same manner as feeding problems.

Constipation occurring during a cold or other illness was not tabulated, nor constipation lasting less than two days.

Mild: irregular movements and occasional laxatives.

Moderate: frequent irregularity, laxatives given once or twice weekly.

Severe: chronic; laxatives given almost daily.

Enuresis: Unlike the other illnesses studied, this was recorded only between 48 and 60 months of age. Both nocturnal and diurnal "accidents" were tabulated.

Other illnesses tabulated included asthma, whooping cough, ear infections, and diarrhea.

Degree of severity was estimated in nine of the illness categories as mild, moderate or severe. Criteria for feeding disorders and constipation have been described. Ratings on other illnesses were based on duration, degree of fever, and medical care required.

Of the thirty-one interval histories sent each family, the following average number of reports were returned and verified by the Fels nurse: singletons, 27.4; first children, 27.9; second children, 27.5. Many of the illnesses reported of course, were based on the diagnosis of the family physician. However, it is recognized that the mothers, who provided much of the raw material for this study, employed many terms in a lay sense, and with the commonly accepted understanding of their meaning. It is further realized that the data may reflect, in part, the parents' emotional attitudes in interpreting the child's somatic symptoms.

Two approaches have been made to an analysis of the data. The *group study* examines illness differentials in incidence and severity in eighty-nine children: twenty-two singletons, thirty-four first children, and thirty-three second children. A second approach to the problem was made by selecting twenty-nine pairs of siblings, who were first and second children in the same family. These children were matched by age and by sequence of interval histories available, and their histories compared. This section of the paper is referred to as the *sibling study*.

RESULTS

The Group Study.—Table I shows the mean incidence, as seen in singletons, first children, and second children, for each illness category. Each group of children shows a distinctive illness picture.

TABLE I. ILLNESS PATTERNS OF SINGLETONS, FIRST CHILDREN, AND SECOND CHILDREN DURING THE FIRST FIVE YEARS OF LIFE

ILLNESS CATEGORY	MEAN NUMBER OF ILLNESSES PER CHILD		
	SINGLETONS	FIRST CHILDREN	SECOND CHILDREN
Respiratory infections	12.91	12.56	16.54
Ear infections	1.23	.74	1.67
Tonsillitis	.14	.38	.39
Whooping cough	.23	.20	.33
Vomiting	2.41	2.68	3.03
Diarrhea	2.50	2.15	3.21
Gastrointestinal disorders	1.50	1.06	1.15
Skin disorders	3.95	3.06	2.82
Accidents	.68	.85	1.18
Feeding disorders	8.54	6.76	6.88
Constipation	5.54	5.00	3.36
Enuresis	.36	.26	1.03
Asthma	.59	.12	.18
Total mean	40.58	35.82	41.77
Total after excluding first four categories (See text)	26.07	21.94	22.84
Number of children in each group	22	34	33

Singletons have the highest mean incidence of miscellaneous gastrointestinal upsets, skin disorders, feeding disorders, constipation, and asthma. Second children have the highest mean incidence in respiratory infections, ear infections, tonsillitis, whooping cough, vomiting, diarrhea, accidents, and enuresis.

First children, on the other hand, do not show the highest mean incidence in any of the illness categories studied. In eight of the items they show the lowest mean incidence.

An analysis was made of the significance of differences between the three groups of children, for each illness category, and also between the singletons and the combined group of first and second children. Those differences which were significant at the 5 per cent level or better are shown in Table II.

TABLE II. DIFFERENCES IN INCIDENCE OF ILLNESS WHICH SHOW STATISTICAL SIGNIFICANCE AT THE 5 PER CENT LEVEL

ILLNESS CATEGORY	HIGHER GROUP	LOWER GROUP
Asthma	Singletons	Combined first and second
Skin disorders	Singletons	Combined first and second
Enuresis	Second Children	Singletons
Enuresis	Second Children	First Children
Diarrhea	Second Children	First Children
Respiratory infections	Second Children	Singletons
Respiratory infections	Second Children	First Children
Combined feeding disorders and constipation	Singletons	Second Children
Combined feeding disorders and constipation	Singletons	Combined first and second
Allergies (see text)	Singletons	Second Children
Allergies (see text)	Singletons	Combined first and second

It will be noted that if the illnesses are taken as a whole, the total mean incidence for second children (41.77) slightly exceeds the total mean for singletons (40.58), and both values are distinctly higher than the mean of 35.82 for first children. If, however, the first four categories of infectious diseases are omitted (respiratory and ear infections, tonsillitis, and whooping cough), the mean incidence for singletons becomes 26.07, for second children 22.84, and for first children 21.94.

From a further inspection of the data, a separate grouping of "allergies" was made, combining allergic skin diseases and asthma. Singletons show a mean incidence of 2.91 cases, first children 1.29, and second children 1.15. The differences between singletons and second children, and between singletons and the combined group of first and second children, are significant at the 5 per cent level.

TABLE III. SEVERITY OF ILLNESS

ILLNESS CATEGORY	PERCENTAGE OF CASES CLASSED AS EITHER MODERATE OR SEVERE		
	SINGLETONS	FIRST CHILDREN	SECOND CHILDREN
Respiratory infections	37	32	38
Ear infections	78	56	53
Vomiting	30	32	29
Diarrhea	42	27	37
Gastrointestinal upsets	27	28	29
Accidents	27	17	28
Feeding disorders	22	29	22
Constipation	37	38	30
Enuresis	50	33	53

In Table III, the three groups of children are compared on the basis of percentage of cases tabulated as either moderate or severe, for each of nine illness categories. For example, each singleton in Table I had an average of 12.91 respiratory infections during the first five years of life. As seen in Table III, 37 per cent of these cases were classed as either moderate or severe.

Little difference is shown between the three groups in severity of vomiting and gastrointestinal upsets. Singletons show greater severity in diarrhea and ear infections, and together with second children, are higher in severity of respiratory infections and accidents. First children show the greatest severity in feeding disorders, and together with singletons, are higher in severity of constipation. Second children are slightly higher than singletons in severity of enuresis, and considerably higher than first children. When severe or habitual enuresis is considered separately, rather than being combined with the moderate category, the distribution is: singletons, 25 per cent; first children, 33 per cent; second children, 47 per cent.

The Sibling Study.—In this section, twenty-nine pairs of siblings were selected, each pair consisting of a first and second child in a family. Forty-six of the fifty-eight children were taken from the group study, and twelve new cases were added. Sixteen pairs of children were like-sexed. In each pair of

siblings, the number and age-intervals of each interval history were matched. The method of comparison of illnesses was essentially the same as in the group study.

TABLE IV. COMPARISON OF ILLNESSES IN TWENTY-NINE PAIRS OF MATCHED SIBLINGS

ILLNESS CATEGORY	MEAN NUMBER OF ATTACKS BY WHICH SECOND CHILD EXCEEDED SIBLING
Respiratory infections	.34
Ear infections	.72
Diarrhea	.48
Feeding disorders	.72
Enuresis	.79
Asthma	.03
Allergies	.03
Accidents	.52
ILLNESS CATEGORY	MEAN NUMBER OF ATTACKS BY WHICH FIRST CHILD EXCEEDED SIBLING
Whooping cough	.03
Vomiting	.41
Skin disorders	.35
Constipation	1.28

No difference: Tonsillitis, gastrointestinal upsets.

Table IV shows the mean incidence of cases by which second children exceed first children in various illness categories, and the number of cases by which first children exceed second children. The results are similar to the group comparisons of the previous section, the only difference being a slightly higher mean incidence of second children in allergies, and a smaller incidence in attacks of vomiting.

In the comparison of severity tabulations, the siblings show much the same pattern as was shown for the groups in Table III.

Thus, the results from the comparison of matched siblings substantially confirm the results of comparisons based on unmatched group samples.

DISCUSSION

The differential distribution of illness categories by ordinal position, as shown in the present study, offers material for speculation. Taylor,² writing on the adjustment problems of the only child, has described a series of longitudinal case studies. Chronic digestive disorders, constipation, anorexia, and skin disorders are included in the illnesses from which singletons tend to suffer. On the other hand, children with siblings were found to be more prone to colds, influenza, measles, mumps, and broken bones. The present findings appear to confirm his results. Taylor suggests that the narrow social environment of singletons, during their critical, formative years, is the causal factor associated with the illness differentials found.

It also seems to be a reasonable hypothesis that illnesses such as asthma, allergies, anorexia, constipation, skin disorders, and gastrointestinal upsets, from which singletons suffer more often than first or second children, may in part be a reflection of a more intense emotional environment created by oversolicitous parents. It has been pointed out by Bakwin and Bakwin³ that singletons, and

to a lesser degree first children, tend to have overprotective, overindulgent, and overanxious parents, and this may frequently be channeled into an abnormal concern over health.

Sontag,⁴ discussing some of the psychosomatic aspects of childhood, states that during infancy and early childhood, physiologic processes are relatively unstable, and even mild stress situations may produce significant degrees of somatic dysfunction. A circular chain of interaction may become established, wherein the parent's anxiety over the child's nutrition, toilet training or illnesses is a source of considerable tension to the child.

A rich background of case histories has been presented by Kanner,⁵ demonstrating the frequency with which parental overprotection may complicate such disorders as constipation, anorexia, and enuresis. Considerable evidence has also been offered^{6, 7} in support of the theory that emotional disturbances may, by lowering the threshold of sensitivity, appreciably influence the character, frequency, and severity of allergic manifestations, such as asthma and some skin disorders.

Concerning the illness patterns of first children, it has been suggested that they may be expected to exceed other groupings of children in those illnesses readily influenced by psychic factors, because of the trauma experienced by the shifting, at the birth of a sibling, from an overprotected life to that of rivalry for parental affection and attention. There is little evidence in our study to substantiate this theory. The first children in our study suffer fewer illnesses than either singletons or second children. They are significantly high only in their incidence of constipation, and in the severity of constipation and feeding disorders. It is possible these two characteristics may be utilized by first children as hostility or attention-getting devices.

The second children in our study show a significantly higher incidence in infectious diseases. Our records also indicate that fewer measures were taken to protect them from such contagious diseases as whooping cough. In addition, the exposure to infection is unavoidably increased because of contact with a sibling.

The high incidence of vomiting and diarrhea in second children often occurred as a concomitant symptom of acute infections. Since anorexia and constipation were not recorded as incidental symptoms of infections, they may be taken to represent functional behavior disorders and are found predominately among the singletons and first children.

The high incidence of accidents among second children may perhaps be attributed to the lessened anxiety on the part of parents, and hence less protection, and to less time available for precautionary measures. It is also possible that competition with an older sibling, when a second child is still physically immature, may increase the latter's accidents, and that an older sibling may sometimes precipitate or inflict injuries on a second child.

Second children significantly exceed both only and first children in the incidence and severity of enuresis. This finding was a somewhat unexpected result.

It could be postulated that younger children, not having yet achieved control of bladder function, may utilize enuresis more often as a method of competing with an older sibling for parental attention. Enuresis may also appear more frequently among second children with an increase in sexual excitement and sex play in the presence of a sibling. It is also possible that enuresis appears more often among younger siblings because it represents an arrest of development rather than a regression. One predisposing environmental factor seems to be lack of adequate training, due to parental overindulgence and carelessness concerning regularity of habits. Enuresis is likely to be excused on the ground that the child is as yet too small to be educated.⁵

First children, on the other hand, may use constipation as their pattern of disability. It is interesting to speculate that constipation, as exhibited in the present study by singletons and first children, and enuresis, as shown by second children, may represent two opposing tendencies in personality development. Constipation may involve control, mastery, withholding, and a kind of masochism, whereas enuresis may reflect self-indulgence, rebellion against control, and giving.

SUMMARY

A comparison was made of the illness records, during the first five years, of twenty-two singletons, thirty-four first children, and thirty-three second children. A similar comparison was made of twenty-nine pairs of matched siblings, consisting of first and second children. Fourteen illness categories are described, and the records for each group, both in incidence and severity of illness, are shown.

Singletons show the highest means incidence in gastrointestinal upsets, skin disorders, feeding disorders, constipation, asthma, and allergies. Second children lead in respiratory and ear infections, tonsillitis, whooping cough, diarrhea, accidents, and enuresis. First children do not show the highest mean incidence in any of the illness categories examined. Those comparisons showing statistically significant differences are indicated.

There is a discussion of the possible significance of the findings, in terms of parental attitudes and interaction of children within the family, and certain hypotheses are suggested to account for the differential distribution of illness categories.

REFERENCES

1. Sontag, L. W. (ed.): *The Fels Research Institute for the Study of Human Development*, Yellow Springs, Ohio, 1946, Antioch College, p. 31.
2. Taylor, L.: *The Social Adjustment of the Only Child*, Am. J. Sociol. 51: 227, 1945.
3. Bakwin, R., and Bakwin, H.: *Psychologic Care During Infancy and Childhood*, New York, 1942, D. Appleton-Century Co., p. 298.
4. Sontag, L. W.: Some Psychosomatic Aspects of Childhood, Nervous Child 5: 296, 1946.
5. Kanner, L.: *Child Psychiatry*, Springfield, Ill., 1946, Charles C Thomas, p. 510.
6. Weiss, E., and English, O. S.: *Psychosomatic Medicine*, Philadelphia, 1943, W. B. Saunders Co., p. 651.
7. French, T., and Alexander, F.: *Psychogenic Factors in Bronchial Asthma*, Washington, 1941, *Psychosomatic Medicine Monographs IV*, p. 92, and *II*, Nos. 1 and 2, p. 236.

SUSTAINED SUMMER HEAT AND FEVER IN INFANTS

HUGO M. CARDULLO, M.D.

NEW YORK, N. Y.

NEW YORK CITY was subjected to a most severe and sustained heat wave during a five-day period in August, 1948. The atmospheric temperatures ranged between 70° F. and 101° F., with a mean of 90° F. for three consecutive days (second, third, and fourth days) and was followed on the fifth day by a mean temperature of 86° F. At the same time the humidity was low. As the heat spell continued, more and more of the infants on the wards of the Children's Medical Service at Bellevue Hospital developed temperature elevations for which no cause could be found by careful clinical and laboratory examinations. Because of the difficulty in determining the role played by the weather, a study was made of the thermal responses of infants under 2 years of age during the heat wave. A number of interesting observations resulted.

REVIEW OF THE LITERATURE

The effect of intense heat upon the adult has been amply evaluated and discussed in the medical literature. The pediatric aspects of the problem however, have not been adequately investigated.

The earliest available reference is by Meyer¹ who, in 1911, noted several cases of heatstroke in infants during an extremely hot summer in Berlin. These amounted to 4.2 per cent of the total number of patients in the Foundling Home during the summer; several terminated fatally. Abt,² in 1919, mentioned that infants have an incompletely developed heat-regulating mechanism whose instability is so marked that ". . . if the room is warm, the temperature may rise to 100° F. or 102° F. or even higher," and that normal and previously healthy children may suffer from heatstroke. Talbot,³ in 1925, stated that ". . . when infants are subjected to excessive heat, their body temperature becomes elevated, they become restless and perspire profusely, and very often the respirations become as high as 186 per minute." In 1926, Adair and Stewart⁴ concluded that high external temperatures at least influence the incidence of fever among newborn infants, and in 1927, Tyson⁵ reported a number of cases of fever in newborn babies which ". . . were probably due to the excessive external temperatures." Dodd and Wilkinson,⁶ in 1927, observed elevated temperatures in a small group of relatively well infants during a week of extreme heat and very little air movement. On the fifth day of excessive heat, a peak of 104.5° F. was reached in one case. Upon removing the patients to a cooler room, their temperatures rapidly returned to normal.

From the Department of Pediatrics, New York University, and the Children's Medical Service, Bellevue Hospital.

Van der Bagert and Moravec,⁷ in 1937, concluded that the temperature-regulating mechanism of children is little less susceptible to environmental changes than is that of the monkey. They stated further that, though the ordinary environment has little effect upon the body temperature of the adult, it has a very definite effect upon the young, and, that the older the child, the more stable is the thermoregulatory center. In 1940, Jones⁸ pointed out an apparent predilection for heatstroke to occur in infancy or beyond the age of 70 years. Åkerren,⁹ in 1943, stated that for purely physical reasons, owing to its small size, and also because of its probably less well-developed cerebral regulatory apparatus, the infant and young child is relatively poikilothermic in comparison with the older child or adult. The most recent report is that of Talbot¹⁰ who, in 1948, concluded that, although physiologic regulation of body heat usually becomes adequate in the first three months of life, it may fail to compensate for extremes of heat and cold for a prolonged period. Throughout childhood most physiologic processes are more easily upset than they are in the mature individual and heat regulation is no exception.

SOURCE MATERIAL

The meteorologic data were obtained from the New York City Weather Bureau.¹¹ No records were kept of the ward temperatures but one may assume that they were at least as high as those reported by the Weather Bureau. In addition, the hospital temperatures probably did not undergo the diurnal variations which were reported for the outdoors. Ferris, Blankenhorn, and Harder,¹² in commenting on studies made by them during a heat wave in Cincinnati in 1938, found that the indoor temperatures were consistently 3° F. higher than those recorded out-of-doors. The explanation offered is that within buildings there is sluggish air movement which prevents dissipation of heat, and that this, in conjunction with the high heat-retaining capacity of construction materials (steel, concrete, etc.), maintains a higher and more stable atmospheric temperature indoors than outdoors.

A total of eighty-eight patients was included in this study. Twenty-four were newborn babies under 10 days of age, and the remaining sixty-four ranged from 10 days to 2 years of age. All temperatures were taken routinely by rectum at 8:00 A.M. and at 4:00 P.M. In the case of the acutely ill patients, and at the height of the heat wave, temperatures were taken every four hours or oftener as indicated. In the various graphs no point was plotted unless it represented the average of the temperatures of at least 70 per cent of the patients in any given group; where the patients within a group numbered less than five, each point is the average of the temperatures of all within the group.

The temperature readings for several days immediately preceding and following the heat wave were included, values being taken from August 22 to September 4, inclusive, for a total of fourteen days. No patient was included who did not have a hospital stay of at least seven days during this two-

week period, but all patients who were admitted because of hyperpyrexia during the heat wave were included in the calculations.

The eighty-eight patients were classified according to diagnosis and divided into five major groups:

I. Newborn infants	24
II. Well boarders	21
III. Congenital or acquired cerebral damage	21
Hydrocephalus and spina bifida	11
Mongolian idiocy	7
Microcephalus	1
Achondroplasia	1
Porencephalus	1
Craniosynostosis	1
Nonspecific birth injury	1
Residual cerebral damage from type 14 pneumococcal meningitis	1
IV. Diarrhea	3
V. Miscellaneous diseases	16
Primary pulmonary tuberculosis	4
Nontuberculous pulmonary disease	2
Miliary tuberculosis	1
Tuberculous meningitis	1
Chronic eczema	1
Spinal deformity	1
Erythroblastosis fetalis	1
Omphalitis	1
Letterer-Siwe's disease	1
Congenital torticollis	1
Congenital cataracts	1
Inguinal hernia	1

GENERAL EFFECT OF THE HEAT

Although the first rise in atmospheric temperature occurred on August 25, there was no significant rise in the average body temperatures until approximately thirty-six hours later, on the afternoon of August 26, when several patients, including the well boarders, developed temperatures above 101.0° F., one patient with hydrocephalus reaching 104.0° F. The three patients with diarrhea differed from the rest in that they showed a marked rise in temperature on the very first day of excessive heat, with individual values ranging between 101.0° F. and 103.4° F. In addition, whereas there was little clinical change among the remaining eighty-five patients, those with diarrhea rapidly deteriorated, appearing dehydrated, ejective, and restless. At the same time the volume and number of watery stools increased.

After the initial thirty-six-hour lag phase, the patients, with few exceptions, showed progressive temperature elevations. Accordingly, a number of antipyretic measures were instituted. These included supplemental water feedings every two hours, removal of all clothing with the exception of diapers, repeated hypodermoclyses of a 3 per cent glucose and 0.3 per cent sodium chloride solution, and blanket orders for 1 gr. of aspirin and cool water sponging of all patients whose temperatures reached 102.0° F. or above.

On the morning of the third day of the heat wave (August 27), the patients were restless, irritable, and were eating poorly, though they took their additional water avidly. None showed evidence of infection. One gram of sodium chloride was added to the twenty-four-hour formulas of all

patients in an attempt to prevent salt depletion from profuse sweating which was noted in a number of babies. Because all formulas are prepared twenty-four hours in advance at Bellevue Hospital, the patients did not receive the additional salt until the following day (August 28). For purposes of control, salt was withheld from six patients, but these were unwittingly selected from among those who seemed to be withstanding the heat best of all. Consequently, no conclusions could be drawn as to the advantages or disadvantages of adding salt. However, somewhat startling results were obtained in those with diarrhea which will be discussed subsequently.

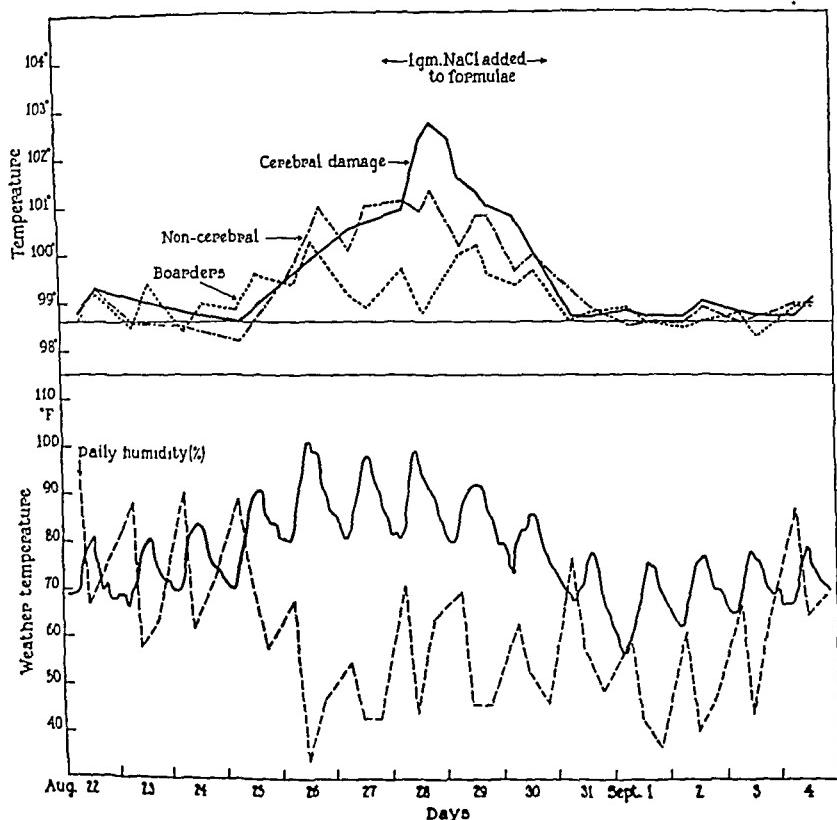


FIG. 1.—A comparison of the temperature responses of well infants, infants with miscellaneous noncerebral diseases, and infants with cerebral defects during the heat wave (Aug. 25 to 29, 1945).

The babies seemed to take their "salted" formulas better for the first two days, but on the third day, when the heat was abating, the older infants refused their feedings. The additional salt was continued through August 30, the first day of relatively normal environmental temperatures.

Despite all measures taken, the temperatures of the patients who had been ill previously, and those of the patients with various forms of cerebral disease, continued to rise until, on August 28, the fourth day of the heat wave, a peak average of 101.3° F. for those with previous illness (Group V) and

102.7° F. for those with cerebral damage (Group III) was reached. The temperatures for the well boarders (Group II), on the other hand, showed no further rise beyond the initial average elevation to 100.3° F. on the second day, although the individual variations ranged as high as 103.0° F. (Fig. 1).

Of the twenty-four patients with cerebral disease six died; of these, four had been in the hospital prior to the onset of the heat wave, and the remaining two were admitted during the period under consideration because of hyperpyrexia.

As the intense heat subsided toward the end of the fifth day, the average temperatures continued elevated for an additional twenty-four hours when normal levels were finally achieved. It is obvious, therefore, that all patients, with the exception of the three with diarrhea, seem to have been capable of adjusting to the abnormal environment during the initial period of the heat wave; when this capacity was lost, fever developed. Similarly, a "cooling off" period of about equal duration followed the recession of atmospheric heat before body temperatures returned to normal.

With the subsidence of the fevers, the irritability, the fretfulness, the poor appetites, and the marked thirsts passed.

EFFECT ON NEWBORN INFANTS

Whereas the temperatures of some fifty normal newborn infants during the ten days immediately preceding the heat wave did not exceed 100.0° F., of the twenty-four normal newborn infants in the nursery during the heat wave, six showed temperature elevations (one as high as 105.4° F.). This is consistent with the report of Adair and Stewart⁴ who found that of 321 babies born during the summer months, 24.3 per cent developed fever. This led them to conclude that the high external temperatures of summer have a definite influence on the frequency of occurrence of fever in newborn infants.

The rise in body temperature in the six infants, which was associated with moderate to marked dehydration, promptly responded to the administration of adequate quantities of fluid. The temperature rises, usually of one day's duration and of a sudden, spiking nature, occurred between the second and fifth days of life. These were not associated with any unusual degree of restlessness or irritability. Salt was not added to their formulas. All infants made uneventful recoveries and were discharged within the usual period of time.

Several reports in the literature^{13, 14} seem to be in accord that the heat-regulating capacity of the mature newborn infant, especially in the responses to excessive heat as contrasted with those toward cold, is fairly well developed, but that it is nevertheless influenced by sustained heat in the absence of adequate quantities of fluid.⁴ Other authors^{2, 3, 7, 8, 10} feel that the thermal regulatory center of the newborn infant is exceptionally labile, but that within a period of weeks or a few months its function, when exposed to extremes of heat and cold, becomes better stabilized.

It would appear that there is a greater degree of thermolability among older infants than in newborn babies inasmuch as a far larger proportion of the former developed fever. However, because of the small total number of patients no conclusions may be drawn.

EFFECT ON WELL BOARDERS

The boarders were a group of healthy and normally developed infants receiving custodial care on the wards of Bellevue Hospital while awaiting return to their homes or placement in foster homes. Of the total of twenty-one, eight were under 6 months of age, eight were between 6 months and 1 year, and five were between 1 and 2 years of age. There were ten girls and eleven boys. The racial distribution was ten white, five Puerto Rican, four Negro, and two yellow.

On August 25, with the first rise in weather temperature, four patients showed a rise above 100.0° F. but none reached 101.0° F.; the remaining seventeen showed no rise whatever. There was no change in their clinical behavior, and the highest average body temperature for this day was 99.6° F. This average temperature was maintained until the early evening of the next day, when it rose to 100.3° F. This was the highest average temperature registered by the boarders throughout the heat wave. On this day, of the twenty-one boarders, six had temperatures above 100.0° F. which ranged between 100.2° F. and 102.8° F. None demonstrated any evidence of infection. Of the six, only one was among the four who had shown an initial rise the preceding day; the temperatures of the other three had returned to normal.

As the heat wave continued unabated, eventually eighteen of the twenty-one boarders showed a rise in temperature; in some the rise was early and gradual, while in others the elevations occurred later and were more sudden in character. A temperature of 101.0° F. or above was registered at some time during the five-day heat period by seventeen patients. In seven cases the temperature rose to 102.0° F. or higher, and on one occasion a reading of 103.0° F. was recorded. There were no convulsions.

The heat wave began to recede on August 30, but the temperatures in this group remained elevated for an additional twenty-four hours before returning to normal. At no time could the rises in body temperatures be attributed to a cause other than the sustained, excessive heat.

The curve for the boarders (Fig. 1) shows the benign course followed by these patients on exposure to prolonged atmospheric heat, as compared with that of the cerebrally handicapped and those who were previously ill. Though their appetites were slightly dulled and their dispositions became moderately difficult, the boarders were at no time a nursing problem and never gave cause for concern.

Sex.—Sex had no significant influence upon the responses of these infants to the sustained environmental heat.

Age.—A comparison of the average temperatures for the three age groups revealed that the temperatures of the youngest were no more affected by the

heat than were those of the patients in the 1- to 2-year range. In agreement with Åkerren,⁹ no conclusion could be drawn as to the stability of the heat-regulatory mechanism in very young infants as contrasted with that of older babies.

Race.—The white, Puerto Rican, Negro, and yellow races were represented. The average temperatures for the patients of each race showed a striking parallelism. This was unexpected since Dodd and Wilkinson⁶ reported that in their series, the two Negro children had been unaffected by the heat, having remained playful throughout, despite having been in a room warmer than that occupied by the white patients. Figuera¹⁵ and Kurrer¹⁶ concluded that Negroes tolerate high external temperatures better than do whites, that they are less susceptible to sun and heatstroke, and therefore body temperature regulation is better in the Negro than in the white individual. Ferris and his collaborators¹⁷ found that whereas the ratio of white to Negro patients among the general hospital admissions during the summer of 1936 was roughly 3:2, the ratio of white to Negro among the patients admitted for heatstroke during a heat wave that same year was 5:1.

Woodruff,¹⁸ on the other hand, pointed out in 1912 that Negroes do not expose themselves in the tropics, and that when they migrate to very hot places they protect themselves with white clothes to prevent heat absorption or soon die. The same author cited a report in which of 146 cases of sunstroke, 13 were blondes, 20 were mixed skin types, and 113 were brunettes, indicating that the more dark-skinned individuals are more susceptible to the effects of heat than are the fair-skinned. He concluded with data from a veterinarian to the effect that in hot weather white horses, which reflect heat, rarely get thermic fever, the deaths being primarily among the animals of dark colors which absorb heat. More recently DuBois¹⁹ showed, by means of a radiometer, that the differences between black and white skins are negligible so far as the radiation of heat is concerned, and that for all practical purposes one may consider the human skin, regardless of color, as a perfect black body radiator.

The small group of cases presented herein does not permit drawing conclusions as to the relative resistance to heat between white and Negro infants, but the impression received is that the Negro baby is no more immune to the effects of heat than is the infant of lighter skin.

From the data presented it may be concluded that healthy, normal infants up to 2 years of age may develop fever as high as 103.0° F. purely from the effects of high external temperatures. All such patients should be closely watched for several days after the recession of the heat wave, since the severe effects of exposure to heat may not appear until after the atmospheric temperature has fallen considerably.^{8, 20}

EFFECT ON PATIENTS WITH CONGENITAL OR ACQUIRED CEREBRAL DAMAGE

The twenty-four patients with congenital or acquired cerebral damage consisted of eleven patients with hydrocephalus and/or spina bifida (of whom only one with spina bifida did not have an associated hydrocephalus), seven

Mongolian idiots, and one each of the following conditions: microcephalic idiot, achondroplasia, craniosynostosis, porencephalus, nonspecific birth injury and residual cerebral damage from a type 14 pneumococcal meningitis.

It was in this group that the most severe hyperpyrexias were encountered (Fig. 1), and it was these patients who posed the greatest nursing and medical problems. Despite the antipyretic measures enumerated one-fourth of these infants succumbed. There were no deaths in any of the other groups.

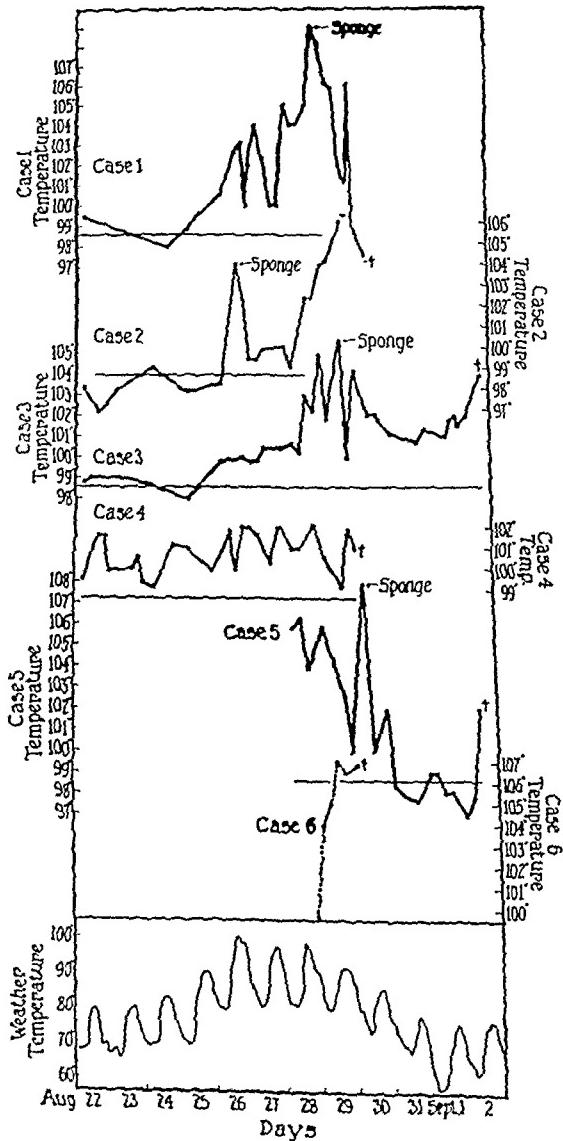


FIG. 2.—Individual temperature curves for six infants with cerebral defects who expired following exposure to sustained environmental heat.

As was the case with the well boarders, these patients had no temperature rise until after thirty-six hours of sustained heat. They were free from infections and had normal temperatures at the onset of the heat wave with the exception of the patient with the craniosynostosis on whom a craniectomy had been performed several days before, and the patient with birth injury who was recovering from an upper respiratory infection; in both the temperatures were rapidly returning to normal. On the evening of August 26, ten of the twenty-four patients showed elevations in body temperature above 100.0° F., with one as high as 104.0° F. Eventually all the patients in the group, except the microcephalic idiot, developed fever, and by the time the atmospheric temperature had subsided fifteen had had fever above 103.0° F.; one infant reached 109.0° F.

The individual temperatures of those who expired are shown in Fig. 2, and they give an indication of the wide excursions in body temperature sustained by those with cerebral defects. It is of interest to note that one of the two patients whose temperature rose to 108.0° F. or above survived the episode.

To correlate the thermal response with the clinical status, the case history of each fatality is briefly summarized.

CASE 1.—J. S., male, white, aged 15 months. Hydrocephalus, meningomyelocele, and paralysis of the lower extremities.

Multiple congenital deformities were found at birth, and the patient was admitted for custodial care at the age of 2 weeks. On admission there was hydrocephalus and a small perforation of the meningomyelocele from which cerebrospinal fluid escaped. Several days after admission the temperature rose to 104.0° F. and was attributed to infection of the meningomyelocele. During the third month of life the spinal defect was repaired surgically. Following this the hydrocephalus expanded rapidly. From the eighth to the tenth month there was periodic, unexplained fever, and the possibility of cerebral fever was entertained. Subsequently, the infant became spontaneously afebrile and followed an uneventful course until the onset of the heat wave. On the second day of sustained heat his temperature gradually rose to 103.0° F. Over the next two days there were wide temperature excursions which responded to aspirin and sponging only temporarily. On the fourth day of the heat wave his temperature rose to 105.0° F. and then to 109.0° F.; the patient appeared dry, pale, and was comatose. Simultaneously there were generalized fine clonic movements. Sweating was absent and the respirations were labored. Despite the repeated sponging and administration of aspirin, the temperature fell to 104.0° F. only briefly, promptly rising to 108.0° F., at which time the convulsions and gasping respirations returned. Physical and laboratory examinations were negative. The following day his temperature was 101.0° F. but rose to 106.0° F. a few hours later. Although sponging was discontinued when 102.0 F. was obtained, his temperature continued to fall. Twelve hours later a body temperature of 97.2° F. was registered and the patient expired shortly thereafter.

CASE 2.—S. B., female, white, aged 3 months. Hydrocephalus, lumbar meningomyelocele, and paralysis of the lower extremities.

The patient was admitted in May, 1948, at the age of 1 week, for evaluation regarding the advisability of surgical intervention for a meningomyelocele. When surgery was deemed inadvisable, she remained in the hospital for custodial

care. Development was slow and definitely retarded in all respects. Enlargement of the head progressed and the lower limbs showed early atrophy. The course was otherwise uneventful until thirty-six hours after the onset of the heat wave, when the temperature suddenly rose to 104.0° F. There was no evidence of acute or chronic infection. The temperature promptly responded to aspirin and sponging, remained normal for about twenty-four hours, and then started upward again. Despite active antipyretic therapy it continued to rise until 106.0° F. was reached on the fifth day of the heat wave, when the patient expired.

CASE 3.—R. J., male, white, aged 18 months. Residual cerebral damage from type 14 pneumococcal meningitis.

The patient had been normal until the tenth month of life when, after an illness of three weeks, he was admitted in January, 1948, and a diagnosis of pneumococcus type 14 meningitis and septicemia was made. Despite intensive chemotherapy, type specific antiserum, etc., the patient remained acutely ill for some thirty days. Finally spinal fluid cultures became sterile and the convulsions which had been present from the onset ceased, but the patient showed evidence of spastic quadriplegia and required feeding via gavage tube. A pneumoencephalogram done on the forty-eighth hospital day revealed massive ventricular enlargement. Until his death, the patient's existence was a vegetative one; all growth and development ceased and feedings could be taken only by gavage. Up to his fifth month in the hospital there were frequent spiking fevers which did not respond to chemotherapy or aspirin, being reducible only by means of sponging or ice water enemas. After the fifth month (May, 1948) the course was afebrile but otherwise unchanged.

Through the third day of the heat wave the patient retained a normal body temperature, but during the next two days his temperature rose abruptly, being only temporarily reduced by repeated sponging and salicylate therapy and reaching 105.8° F. There were no convulsions and the physical examination was noncontributory. As the weather heat subsided, the patient's temperature ranged between 100.0° F. and 102.0° F. for several days. Then on September 2, three days after the return of normal environmental conditions, the temperature rose to 104.0° F. and the patient expired.

CASE 4.—Jn. St., male, white, aged 8 months. Hydrocephalus, meningo-myelocele, talipes equinovarus, and paralysis of the lower extremities.

The patient did well until the third day of life when he developed Cheyne-Stokes respirations, refused feedings, and had a temperature ranging between 100.0° F. and 106.0° F. A diagnosis of subdural hematoma was made and was confirmed when the patient was transferred to Bellevue Hospital. Cerebrospinal fluid cultures were sterile. Within a few days the condition improved and a relatively uneventful course followed. There were two episodes of respiratory distress which followed closely upon feeding and were considered due to aspiration. The head circumference increased rapidly in size for the first few months. On occasion a temperature of about 101.0° F. would persist for several days with no apparent reason; subsidence was always spontaneous. Just prior to the onset of the heat wave the patient had apparently entered upon a similar episode with temperature ranging between 99.2° F. and 101.2° F. As the environmental temperature rose and persisted, the patient became restless but showed no appreciable further elevation of temperature. On August 30 his temperature was 102.0° F.; he was cyanotic and was convulsing. He expired within a few moments. Inasmuch as this occurred shortly after feeding and no permission for necropsy was granted, exitus from aspiration cannot be ruled out though no untoward incident was noted during the feeding.

CASE 5.—L. L., female, white, aged 15 months. Mongolian idiocy.

This seriously retarded infant had always been very irritable, but in the two days preceding admission (third and fourth days of the heat wave) had become markedly more so. She had had frequent bouts of unexplained fever since birth, but with this illness the fever was higher than usual; she took food and fluids poorly, and had repeated tonic seizures. On the fifth day of the heat wave she was admitted to the hospital in coma with a temperature of 104.8° F., marked intermittent nuchal rigidity, noisy respirations, dullness over the right upper chest anteriorly, and coarse rhonchi throughout all lung fields. The skin was hot and dry. All laboratory findings were within normal limits. There was no reduction in body temperature despite intensive therapy throughout the ensuing twenty-four hours. On the following day there was extensive impairment of the percussion note and profuse moist râles bilaterally. Then there was a transient temperature fall to 100.0° F. which was followed by an abrupt rise to 108.0° F. with concomitant tonic and clonic convulsions, cyanosis, and coma. Continuous sponging finally succeeded in reducing the fever. With the return of normal environmental temperatures, the patient's temperature remained at normal and subnormal levels for forty-eight hours though she never roused from the stuporous state. On September 3, the temperature suddenly rose to 102.0° F. and the patient expired.

CASE 6.—J. G., female, white, aged 8 months. Mongolian idiocy, left chronic otitis media.

The patient had been well until the day before admission, which was the fourth day of the heat wave, when a high fever appeared with rapid respirations and a slight cough. She took food and fluids poorly. On the morning of admission, August 30, her temperature was 106.8° F.; she appeared acutely ill, and her respirations were 120 per minute. The fontanel was slightly sunken, the mucous membranes were dry, and the left eardrum was retracted. The chest was dull over the right base anteriorly and many small inspiratory râles were heard over the same area. The liver edge was palpable 2½ cm. below the costal margin. The skin over the upper chest and arms had a fine, diffuse miliaria-like eruption, and was hot and dry. There were no convulsions. A hypodermoclysis of 100 c.c. 3 per cent glucose and 0.3 per cent sodium chloride solution was immediately given and 1 gr. of aspirin was administered. Before the therapy could have effect, the patient died.

At autopsy the pertinent findings consisted of dilatation of all the chambers of the heart and interauricular and interventricular septal defects; the entire left lung and the right lower lobe were firm and reddish-blue with gray and dark red patches. On pressure moderate amounts of clear fluid could be expressed. Microscopic examination of the lungs showed marked congestion of the alveolar capillaries with patchy outpouring of red blood cells and edema fluid into the air spaces. Within the air spaces there were large numbers of mononuclear and multinuclear giant cells. There was a moderate degree of fatty change in the liver cells, most marked in the periportal areas and diminishing toward the central vein. The sinusoids were somewhat distended and filled with blood. The splenic pulp was congested and there was an increase in the total number of polymorphonuclear leucocytes. The adrenal cortical cells were pale and not well vacuolated. At the corticomedullary junction and within the medulla there was evidence of fresh hemorrhage.

The pathologic diagnosis was: Mongolian idiocy, congenital heart disease, congestion and edema of the lungs with hemorrhagic lobular pneumonia, fatty change and congestion of the liver, chronic passive congestion of the spleen and hemorrhage into the adrenal medulla.

There is no striking difference in the incidence of thermal fever among the boarders and the infants with cerebral damage. What is arresting, however, is the marked contrast in the character and intensity of the thermal responses of the two groups, and the absence of fatalities in the one group and the death of one-fourth of the patients in the other. Poikilothermia in the presence of cerebral damage in infants has been reported by several authors.^{9, 21, 22} There is experimental evidence to indicate that hydrocephalus predisposes to altered function of the thermoregulatory center. Bazett and Penfield,²³ in 1922, showed that following decortication, cats retain no temperature control. If the decortication is unilateral the thermoregulatory center remains unaffected; but if, in these unilaterally decorticate cats, the remaining brain matter is subjected to some pressure (i.e., wax), the raised intracranial pressure readily destroys the power of temperature control.

Akerren⁹ emphasized the marked tendency of infants "stigmatized" in some way by congenital or acquired morbid conditions such as mongolism, spasticity, hydrocephalus, etc., to develop highly febrile reactions to infections, and concluded that hyperpyrexia may be both a cause and a result of cerebral injuries.

The evidence for pneumonic involvement in two of the six fatalities might raise the question of the validity of attributing these deaths to the excessive heat. However, it has been pointed out⁹ that although the combination of dyspnea, cyanosis, pallor, and very high fever simultaneous with catarrhal symptoms would suggest a severe pulmonary infection such as capillary bronchitis or bronchopneumonia, the actual pulmonary involvement may prove to be extremely meagre. The same author continues that the unfavorable effect which hyperpyrexia has on the organs of respiration and circulation, especially in the presence of convulsions and coma, is likely to favor the appearance of grave affections of the air passages, especially if the patient has already suffered from an infection of the upper passages or pharynx. In a patient with severe involvement of the air passages associated with hyperpyrexia, it does not necessarily follow that the high fever is secondary to the respiratory pathology; the causal relation may be the reverse. Some authors^{19, 20, 24} have reported that the post-mortem examination of patients who died of heatstroke almost always reveals chronic congestion and edema of the viscera, especially of the lungs and brain. Horanyi-Hechst²⁵ found that in simple deaths from heat as it occurs in cases of heatstroke or in experimental overheating of animals, severe cerebral symptoms in the form of loss of consciousness, paralysis, convulsions, hyperpnea, and tachycardia are characteristic; at autopsy the animals demonstrated hemorrhages and hyperemia in both the meninges and the vessels of the brain substance. McKenzie and LeCount,²⁶ in their post-mortem studies on thirty-seven patients who died of heat stroke, found the following quite regularly: edema of the brain and/or leptomeninges with associated hyperemia of the lungs, lessened substance of the suprarenal cortices, hyperplasia of the spleen, cloudy swelling of the liver, the kidneys, and myocardium, and petechial hemorrhages of the mucous membranes and of the skin. It has also been reported,²⁷ however,

that pneumonia of the upper lobes is one of the commonest predisposing factors in the development of hyperpyrexia in excessively hot weather.

In the light of these findings, therefore, it is not unwarranted to conclude that the external heat was the primary causative element in the deaths of these infants.

EFFECT ON PATIENTS WITH DIARRHEA

There were three patients who had diarrhea during the period of the heat wave. In two of these, the diarrhea was associated with an otitis media and an upper respiratory infection. Stool cultures were repeatedly negative for intestinal pathogens. Prior to the onset of the heat wave (August 22 to 24), these patients had two to six bulky, watery, yellow stools a day, were afebrile, and only slightly dehydrated. They all showed a moderate degree of weight loss. Penicillin and sulfadiazine were given as indicated. Following the suggestions of Chung and Viscorova,²⁸ feedings were given as tolerated throughout the course of the illness. The oral feedings and supplementary parenteral fluids were given in amounts which insured a total daily intake of approximately 200 c.c. fluids per kilogram per day. The total fluids were calculated to supply the patient with from 2 to 3 Gm. of sodium chloride per day and an adequate amount of potassium.

Table I shows the actual fluid intake (in cubic centimeters) of these patients during the days indicated. Any vomitus has been estimated and deducted from the total intake. In general the fluid intake was adequate.

TABLE I

PATIENT	WEIGHT (LBS.)	8/24	8/25	8/26	8/27	8/28	8/29	8/30
M.M.	14	---	420	1420	1370	1330	1160	840
G.R.	11	840	720	1320	900	1280	750	1110
M.O.	5½	440	560	720	900	820	255	450

In contrast to the others in this series, the patients with diarrhea showed a sudden rise in body temperature within twelve hours of the onset of the heat wave, for an average reading of 101.6° F. on the evening of August 25. Their clinical condition rapidly deteriorated though there was no evidence of a superimposed infectious process. They appeared cachetic, dehydrated, and their stools became projectile and increased in number and volume. In one patient (M.M.) vomiting appeared for the first time and, because of its severity, oral feedings were withheld. Little or no response was noted upon intensification of the antipyretic and fluid therapy.

On the fourth day of the heat wave 1 Gm. of sodium chloride was added to the formulas of these patients as well as to the others. All three took their formulas well, including the patient whose vomiting had previously been quite serious. The following day, approximately thirty hours after instituting the extra gram of salt, all three patients showed a dramatic drop in fever and general improvement despite the continued heat and no further change in therapy. (Fig. 3.) The number and character of the stools improved from this time on; the patients ceased to be the serious problem they had been, and went on to uneventful recoveries.

Summer diarrhea in infants has long been recognized as a definite, though somewhat nebulous, entity. Abt² commented that children who have suffered frequent insults from gastrointestinal diseases during the summer are liable to acute exacerbations of intestinal intoxication associated with high fever and marked losses of weight. This is understandable since the younger child tolerates water loss less well than the older child, and the combination of fever, poor fluid intake, and diarrhea readily lead to an anhydremia which is most difficult to treat. It has been shown²⁹ that as the temperature range or mean temperature rises above its ordinary summer level, there is likely to be a rise in the diarrhea and enteritis infant mortality rate.

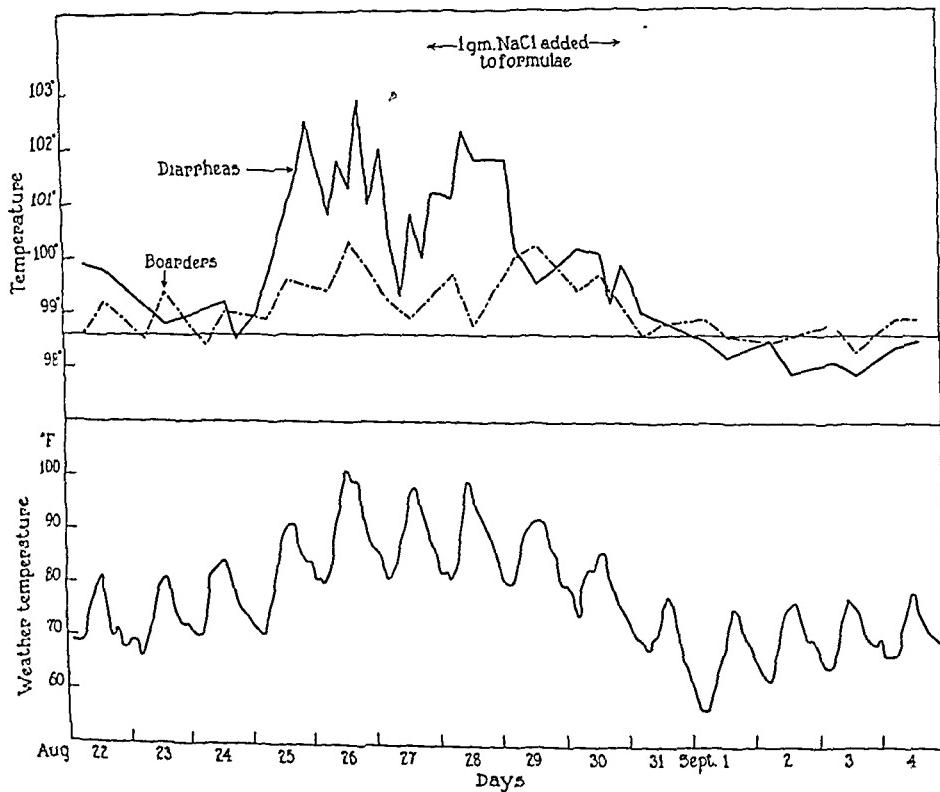


Fig. 3.—A comparison of the temperature responses of well infants and infants with diarrhea during the heat wave (Aug. 25 to 29, 1948).

The average temperature curve for those with diarrhea differs markedly from that of the remainder of the patients. Their temperatures rose within twelve hours of the onset of the heat wave, whereas the other patients showed no rise until after approximately thirty-six hours of sustained environmental heat. This observation suggests that in diarrhea the state of anhydremia makes the patient especially susceptible to the effects of atmospheric heat, inasmuch as this added factor unduly taxes the already faltering thermoregulatory mechanism. Consequently, as for all the previously discussed patients, strenu-

ous efforts must be instituted early to prevent the additional influence of heat on patients with diarrhea.

Of particularly interest is the fall in body temperature and general clinical improvement which occurred within thirty hours of the institution of additional salt. Several investigators^{19, 20} have reported that since the blood sodium chloride levels are normal in cases of heatstroke, and that there is failure to respond to saline administration,²¹ salt dissipation or need plays little if any part in the syndrome. Miller,²² on the other hand, believes it is reasonable to assume that since the largest part of the approximately 100 Gm. of sodium chloride in the average (adult) human body is to be found in the extracellular compartment, a considerable amount of chlorides can be lost without a corresponding lowering of the blood chloride level which the organism tenaciously attempts to maintain.

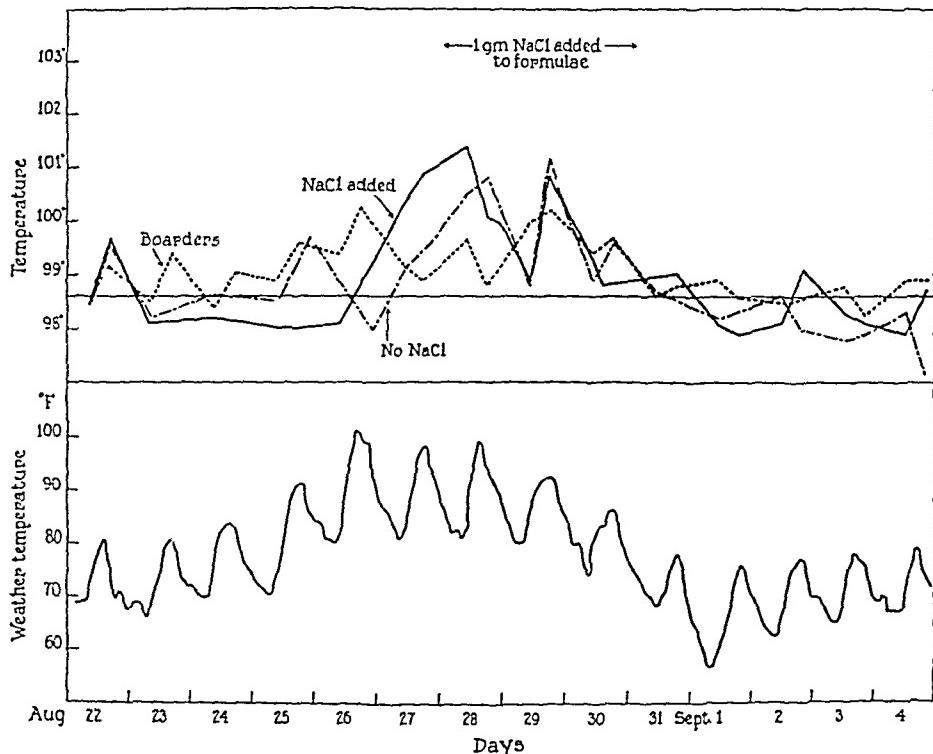


Fig. 1.—A comparison of the temperature responses of well infants with primary pulmonary tuberculosis to whose formulas 1 Gm. sodium chloride was added, and infants with primary pulmonary tuberculosis to whose formulas no sodium chloride was added.

The febrile course of the patients without diarrhea to whom additional salt was administered was unaffected. A comparison between two patients with primary tuberculosis who received additional salt and two similar patients who received no salt reveals no difference in the intensity and type of temperature curve traced. (Fig. 4.)

The significant fall in body temperatures in those with diarrhea when the temperatures of the other patients were still markedly elevated suggests a beneficial effect from the additional salt in this condition. However, no further conclusions may be drawn until further and more extensive studies are carried out.

EFFECT ON MISCELLANEOUS DISEASES

There was a total of sixteen patients in this group which included conditions such as primary pulmonary tuberculosis, miliary tuberculosis, tuberculous meningitis, bronchopneumonia, congenital lung cyst, chronic eczema, spinal deformity, erythroblastosis fetalis, inguinal hernia, congenital cataracts, congenital torticollis, Letterer-Siwe's disease, and omphalitis.

As a group, they showed febrile responses to the environmental heat midway between that of the patients with cerebral damage and that of the well boarders. The character of the average curve was similar to that of the other two groups (Fig. 1). It is of interest that the highest fevers were found in the patients with the infected congenital lung cyst and with bronchopneumonia. The remainder of the patients, whose afflictions were essentially of a chronic nature, developed fevers which were, in general, slightly lower.

From the findings in this group it may be concluded that in the presence of pre-existing pathology which is not cerebral in origin the thermal response to sustained environmental heat will be somewhat higher than that encountered in previously healthy infants, but well below that of patients who have diffuse cerebral damage.

THERAPY

It is quite obvious that for cerebrally handicapped patients strenuous measures must be taken to forestall the development of hyperpyrexia during heat waves. To await its development to institute therapy may be disastrous, for once the body temperature in these patients begins to rise, all efforts will prove futile in a large percentage of the cases. If it is not feasible to remove these infants to a cooler environment, more normal surroundings must be created for them by the use of fans, ice, frequent cool baths, etc. In addition, any pre-existing infection must be vigorously combated and brought under control at the earliest possible time. Similarly, steps must be taken to prevent exposure to individuals who harbor acute infections, especially those of the respiratory tract.

If the body temperature has already risen every effort should be made to promote heat loss. Of primary importance is the reduction of the environmental temperature, which may be accomplished by the various methods already suggested. Also, the clothing should be completely removed and 1 gr. of aspirin should be administered every four to six hours. These measures should be instituted promptly and continued as long as the environmental temperature remains elevated and for several days thereafter.

Although stressed for those with cerebral damage, the measures outlined should be applied to all infants, normal as well as diseased, during periods of sustained heat.

DISCUSSION

The data presented indicate that the majority of infants under 2 years of age will develop fever when exposed to sustained atmospheric heat. The intensity of the fever depends upon the individual patient's state of health prior to the exposure. The thermoregulatory apparatus of the normal infant, though labile, is capable of withstanding prolonged excessive heat and of protecting the individual from its effects. However, where there exists severe functional or organic brain damage, the heat-regulating center is unable to cope with the demands imposed upon it, and heatstroke frequently ensues. Whether the defect lies in the vasomotor system^{31, 33-38} in the sweating mechanism,^{19, 31, 38-47} or primarily in the central heat-regulating organ, the hypothalamus,⁴⁸⁻⁵⁴ cannot be said. It is known, however, as Sutton⁵⁵ pointed out in 1909, that once the mechanism of heat regulation in the human body has been definitely upset by high external temperature, a vicious cycle is established. When the internal temperature rises, the processes of oxidation (in accord with van't Hoff's law), and therefore the production of heat, also increase, so that the body temperature rises still further, and so on. Consequently, the main problem lies in preventing the initiation of such a cycle.

If it is assumed that the factors of heat production (activity, basal metabolic rate, and calorigenic action of food) were similar for all patients, and since the amount of heat lost to the surroundings by convection and radiation was the same because of exposure to identical environmental conditions, there remains but one factor for heat dissipation where individual variations may have accounted for the vast differences in body temperatures. That factor is sweating. Unfortunately, no records were kept of which patients perspired and which did not, and consequently no comment can be made on the subject, but it seemed to be the general impression that sweating was least observed among those with the highest body temperatures. Investigations along these lines are being planned at present.

SUMMARY

A clinical study of the thermal responses of eighty-eight patients under 2 years of age was made during a five-day heat wave in New York City in the summer of 1948. The following conclusions were drawn:

1. In the majority of infants under 2 years of age, the body temperature rises when exposed to sustained environmental heat.
2. This elevation may exceed 103.0° F. in normal, healthy infants (including mature newborn infants), in the absence of any evidence of acute infection.
3. Under 2 years of age there is no apparent correlation between age, sex, or color and the susceptibility to develop thermal fever.
4. Usually there is a lag phase of thirty-six or more hours from the onset of the atmospheric heat to the rise in body temperature. Similarly, the fever may not subside until twenty-four or more hours after the external temperatures have returned to normal levels.

5. Patients with diarrhea seem to develop fever sooner than normal or otherwise ill infants. It is suggested that additional alimentary salt may be beneficial in restoring the body temperature of infants with diarrhea to normal levels.

6. A pre-existing acute or chronic infection, especially of the respiratory tract, predisposes to the development of high fever upon exposure to sustained environmental heat.

7. In infants with congenital or acquired cerebral defect, there exists a marked tendency to the development of hyperpyretic states and to heat stroke. The temperature may rise to 109.0° F. and the mortality is high.

8. These fevers are exceptionally resistant to antipyretic measures once they become established. Consequently, prevention is the keystone of successful therapy.

REFERENCES

1. Meyer, L. F.: Die Morbidität und der Mortalität der Säuglinge im Sommer, Deutsche med. Wehnschr. 37: 2090, 1911.
2. Abt, I. A.: Temperature Variations in Infancy and Early Childhood, Illinois M. J. 36: 5, 1919.
3. Talbot, F. B.: Body Temperature and its Regulations, in Abt's Pediatrics, Philadelphia, 1925, W. B. Saunders Co., vol. 6, p. 8.
4. Adair, F. L., and Stewart, C. A.: Fever in the Newborn Infant, Am. J. Dis. Child. 31: 846, 1926.
5. Tyson, R. M.: Fever in the New Born, Am. J. Dis. Child. 34: 979, 1927.
6. Dodd, Katherine, and Wilkinson, S. J.: External Heat a Cause of Fever in Children, J. A. M. A. 88: 787, 1927.
7. van der Bagert, F., and Moravec, C. L.: Body Temperature Variations in Apparently Healthy Children, J. PEDIAT. 10: 466, 1937.
8. Jones, P. H., Jr.: Effects of High Environmental Temperature on the Human Body, New Orleans M. & S. J. 93: 6, 288, 1940.
9. Akerren, Y.: On Hyperpyretic Conditions During Infancy and Childhood, Acta Paediat. 31: 1, 1943.
10. Talbot, F. B.: Temperature Regulation in Health and Disease, in Brennemann's Practice of Pediatrics, vol. I, Hagerstown, 1948, W. F. Prior Co., chap. 5, p. 1.
11. U. S. Department of Commerce Weather Bureau Monthly Meteorological Summary of New York, N. Y., for August and September, 1948.
12. Ferris, E. B., Jr., Blankenhorn, M. A., and Harder, F. K.: Factors Concerned in the Geographical Distribution of Heat Stroke in Cincinnati, J. Med. 19: 245, 1938.
13. Mendelsohn, A.: The Capacity for Heat Regulation in Infants, Ztschr. f. Kinderh. 5: 269, 1912.
14. Anderson, J. A.: Effects of Relative Humidity on Skin and Rectal Temperatures of the New Born Infant, Proc. Soc. Exper. Biol. & Med. 44: 466, 1940.
15. Figueras, L.: Insolación y aclaramiento, Siglo medico 68: 286, 1921.
16. Kurrer, A.: Ueber Temperaturerholungen bei Heizern, Deutsche Vrtljschr. f. öff. Gesundheitspfleg. 21: 291, 1892.
17. Ferris, E. B., Jr., Blankenhorn, M. A., Robinson, H. W., and Cullen, C. E.: Heat Stroke: Clinical and Chemical Observations on 44 Cases, J. Clin. Investigation 17: 249, 1938.
18. Woodruff, C. L.: Blondes and Brunettes in the Tropics, New York M. J. 96: 721, 785, 1912.
19. Dubois, L. F.: The Mechanism of Heat Loss and Temperature Regulation, Lane Medical Lectures, London, 1937.
20. Wilcox, W. H.: The Nature, Prevention and Treatment of Heat Hyperpyrexia, Brit. M. J. 1: 392, 1920.
21. Mader, A.: Regulatory Dysfunction of the Thermogenetic Apparatus of Malformed Newborn Infants, Jahrb. f. Kinderh. 98: 105, 1922.
22. Urwitz, S.: Contribution to the Literature on Thermoregulation (With Special Reference to 2 Infants With Deformity of the Brain), Acta Paediat. 33: 158, 1946.
23. Buzett, H. C., and Penfield, W. G.: A Study of the Sherrington Decerebrate Animal in the Chronic as Well as the Acute Condition, Brain 45: 185, 1922.
24. Moschowitz, A. V.: Post operative Heatstroke, Surg. Gynec. & Obst. 23: 443, 1916.

25. Horanyi-Hechst, B.: Ueber die Wirkung der experimentellen Hyperthermie auf das normale Nervengewebe, *Arch. f. Psychiat. u. Nervenkrankh.* 104: 256, 1935.
26. McKenzie, P., and LeCount, E. R.: Heat Stroke (With a Second Study of Cerebral Edema), *J. A. M. A.* 71: 260, 1918.
27. Park, R. G.: Disorders Due to Heat, *New Zealand M. J.* 44: 128, 1945.
28. Chung, A. W., and Viseorova, B.: The Effect of Early Oral Feedings Versus Early Oral Starvation on the Course of Infantile Diarrhea, *J. PEDIAT.* 33: 14, 1948.
29. Gafasir, W. M.: Infant Diarrhea and Enteritis and Climate, London 1876-1927, *Am. J. Hyg.* 11: 535, 1930.
30. Wolkin, J., Goodman, J. I., and Kelley, W. E.: Failure of the Sweat Mechanism in the Desert (Thermogenic Anhydrosis), *J. A. M. A.* 124: 478, 1944.
31. Lee, D. H. K.: The Human Organism and Hot Environments, *Tr. Roy. Soc. Trop. Med. & Hyg.* 29: 7, 1935.
32. Miller, M. M.: Letter in *J. A. M. A.* 124: 1152, 1944.
33. Wells, G.: The Effect of External Temperature: Changes on Heart Rate, Blood Pressure, Physical Efficiency, Respiration and Body Temperature, *Research Quart. Am. Phys. Ed. Assn.* 3: 108, 1932; 4: 162, 1933.
34. Laurens, H.: The Regulation of Body Temperature, *New Orleans M. & S. J.* 93: 6:283, 1940.
35. Taylor, H. L., Henschel, A. F., and Keys, A.: Cardiovascular Adjustments of Man in Rest and Work During Exposure to Dry Heat, *Am. J. Physiol.* 139: 383, 1943.
36. Ribadeau-Dumas, H., Tardieu, G., and Renard, Mme.: The Function of the Glomus in the Thermal Regulation of the Newborn, *Bull. Acad. nat. Méd.* 130: 47, 1946.
37. Adolph, E. F., and Associates: Physiology of Man in the Desert, New York, 1947, Interscience Publishers, Inc.
38. Brooks, C.: The Regulation of Body Temperature, *M. J. Australia* 1: 221, 1948.
39. Hill, L.: Physiological Aspect of Heat Stroke, *Brit. M. J.* 1: 397, 1920.
40. Kuno, Y.: The Physiology of Human Perspiration, London, 1934, J. & A. Churchill, Ltd.
41. Day, R.: Respiratory Metabolism in Infancy and Childhood. XXVII. Regulation of Body Temperature in Premature Infants, *Am. J. Dis. Child.* 65: 376, 1943.
42. Winslow, C. E. A., Herrington, L. P., and Gagge, A. P.: Physiological Reactions of the Human Body to Varying Environmental Temperatures, *Am. J. Physiol.* 120: 1, 1937.
43. Engelhardt, H. T., and Melvin, J. P., Jr.: General Acquired Anhidrosis, *Am. J. M. Sc.* 210: 323, 1945.
44. Blankenhorn, M. A., Ferris, E. B., Cullen, C. E., and Robinson, H. W.: Heat Stroke: A Clinical Study, *J. Clin. Investigation* 16: 659, 1937.
45. Adolph, E. F.: The Initiation of Sweating Response to Heat, *Am. J. Physiol.* 145: 710, 1946.
46. Brobeck, J. R.: Physiology of Heat and Cold, *Ann. Rev. Physiol.* 8: 65, 1946.
47. Weech, A. A.: Hereditary Ectodermal Dysplasia, *Am. J. Dis. Child.* 37: 766, 1929.
48. Wilbur, R. L.: Abnormal Body Temperatures in Injuries of the Cervical Spinal Cord, *California State J. Med.* 9: 495, 1911.
49. Keller, A. D., and Hare, W. K.: Heat Regulation in Medullary and Mid-Brain Preparations, *Proc. Soc. Exper. Biol. & Med.* 29: 1067, 1932.
50. Keller, A. D., and Hare, W. K.: The Hypothalamus and Heat Regulation, *Proc. Soc. Exper. Biol. & Med.* 29: 1069, 1932.
51. Ranson, S. W.: Some Functions of the Hypothalamus, Harvey Lecture December 1936, *Bull. New York Acad. Med.* 13: 241, 1937.
52. Ranson, S. W., Fisher, C., and Ingram, W. R.: Hypothalamic Regulation of Temperature in the Monkey, *Arch. Neurol. & Psychiat.* 38: 445, 1937.
53. Clark, G., Magoun, H. W., and Ranson, S. W.: Hypothalamic Regulation of Body Temperature, *J. Neurophysiol.* 2: 61, 1939.
54. Erickson, T. C.: Neurogenic Hyperthermia, *Brain* 62: 172, 1939.
55. Sutton, H.: The Influence of High Temperatures on the Human Body, Especially With Regard to Heat Stroke, *J. Path. & Bact.* 13: 63, 1909.

ILLNESSES WITHIN THE FIRST YEAR OF LIFE

MILDRED A. NORVAL, M.D., AND ROGER L. J. KENNEDY, M.D.
ROCHESTER, MINN.

ALTHOUGH the morbidity rate is said to be highest in the first year of life, few articles in the literature supply definite information about illnesses in this period. The purpose of this paper is to present data obtained in a study of illnesses that occurred among 417 infants during their first year of life.

Illness was interpreted as a continuous period of "infection" regardless of complication. This definition ruled out such conditions as infantile colic, injuries, operations, the more simple dermatologic conditions, and congenital defects such as clubfeet. If one condition was reported as the primary cause and was associated with other conditions, only the primary cause was tabulated. If there was more than one cause of illness, the disease most specifically associated with the period of sickness was preferred over a minor condition which preceded or accompanied it. Records obtained in this manner were of the incidence of attacks rather than of illnesses in the sense of chronic ill-health.

The infants in this series were born of residents of Rochester, Minn., during 1944 through 1946. Owing to the uniquely coordinated program of medical care for children in this city, most of the infants are seen at a well child clinic each month during their first year of life. For their more serious illnesses most of these children are attended by a pediatrician. To be assured that the information concerning the illnesses was collected from the infants' mothers at frequent intervals, only those infants were selected who had attended the Well Child Clinic at least nine times during their first year of life. At each of these conferences with the mother, the physician inquired about any illnesses that the child might have had since his last visit, and recorded the diagnosis, approximate date, and whether a physician attended the child during the illness. As a check that all illnesses were reported, the pediatricians' records on these children were reviewed and a record of any additional illnesses was inserted. This selection of infants does eliminate the few children who were chronically ill and needed prolonged care by a pediatrician, or who might have died before the end of the first year, but we have included any illness that was observed by the mother, no matter how mild.

Among this group of 417 infants there were recorded 679 illnesses, which were distributed equally between the boys and the girls. This is not in agreement with the illness study by Collins,¹ who found the illness rates for males to be consistently greater than those for females except in the age period 1 to 2 months. Data for his study were obtained from five different illness studies conducted by periodic canvasses of families within the past twenty-five years.

From the Department of Pediatrics, Mayo Foundation and Mayo Clinic.

In each survey the families were visited at intervals of two to four months, and a record was made of any illness of the infants under observation by month of age up to twelve months. Falk and his associates² had found in a public health survey that illnesses in the first fifteen years of life were equally distributed between the two sexes. Illness was defined by Falk as "any disorder that wholly or partially disabled an individual for one or more days or as an experience for which medical service of any kind is received. Any condition, symptom or disorder for which drugs costing fifty cents or more are purchased is considered an illness."

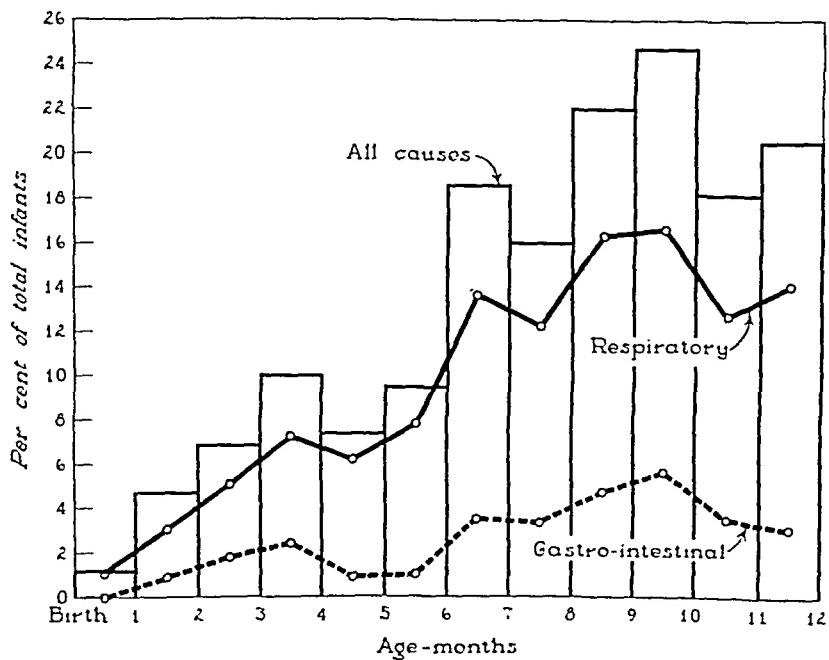


Fig. 1.—The incidence of illness in relation to the age of the infant.

The incidence of illness for this group of infants was 1.63 per infant for the age period studied. This is a higher incidence of illness than was found by Falk and his associates, Collins, or Sydenstricker,³ but lower than Stevenson⁴ reported. Falk found that the incidence rate of illness during the first year of life varied between 1.29 and 1.39 per infant depending on the income level of the families. Collins found an illness rate of 1.45 per person for infants less than 1 year of age. In the Hagerstown morbidity study,³ the rate was 1.59 per person for children less than 5 years of age. Stevenson found among 263 infants in Boston, who were carefully followed in a longitudinal study of child health and development, that the average number of infections per infant varied from 1.79 to 2.43 per year according to the method of feeding. Some variations in the reported incidence rate of illness can be accounted for by different definitions of illness, the variety of income groups surveyed, the geographic location of the subjects, and the ages of the individuals observed.

Of the 417 infants in this series, 22.8 per cent were reported as not being ill during their first year of life, 28.5 per cent had one illness, 26.2 per cent had two illnesses, and 22.5 per cent had three or more. Among nearly 40,000 persons of all ages, Collins found that 48 per cent did not suffer from illness during a year, 32 per cent were ill once, 13 per cent twice, and 7 per cent three or more times. Similar figures were obtained by Falk and his associates from a study of members of 9,000 white families in seventeen states.

The distribution of illnesses according to the age of the infant is shown in Fig. 1. There is a steady rise in the number of illnesses from all causes as the infants approach their first birthday, as well as in the illnesses due to respiratory and gastrointestinal disease. The illnesses during the last six months of the first year are approximately three times the number during the first six months of life; this increase is of the same order among the respiratory and the gastrointestinal diseases. Grulee and his associates^{5, 6} investigated the morbidity from infections among 20,000 artificially-fed and breast-fed infants who were followed for as long as nine months by Chicago's Infant Welfare Society during 1924 to 1929. They found a rise in the illness rate each month until the fifth month with all types of infant feeding; the rate then decreased in the breast-fed and partially breast-fed groups but in the artificially-fed group the rise continued through the ninth month. Collins found that illnesses from all causes start with a high rate for the first month of life and drop to the lowest rate in the second month, followed by a gradual increase to a level of about 1.5 illnesses per infant throughout the last half of the first year of life. The digestive diseases had a high rate in the first month of life; then the rate fell rapidly and remained quite stable throughout the first year, while the respiratory diseases increased during the period observed.

It has been generally recognized that respiratory infections and gastrointestinal illnesses are the principal causes of illness in this age period. In Table I are shown the illnesses during the first year of life. In this group respiratory

TABLE I. CAUSES OF ILLNESS WITHIN THE FIRST YEAR OF LIFE

	CASES	PER CENT OF TOTAL
Respiratory diseases	495	72.9
Coryza, "cold," pharyngitis, tonsillitis, and upper respiratory infection	388	57.1
Otitis media with respiratory infection	36	5.3
Laryngitis	12	1.8
Bronchitis	42	6.2
Influenza	13	1.9
Pneumonia	4	0.6
Gastrointestinal diseases	130	19.1
Diarrhea	93	13.7
Gastroenteritis	37	5.4
Contagious diseases		
Chickenpox	29	4.3
Rubella	9	1.4
Whooping cough	7	1.1
Rubeola	6	0.9
Poliomyelitis	3	0.4
Mumps	3	0.4
Rosacea infantum	1	0.1
Other	19	2.8
	6	0.9

disease was the most frequent and accounted for 72.9 per cent of the illnesses. Coryza, "cold," and infections of the respiratory tract comprised almost 86 per cent of the respiratory illnesses. In Sydenstricker's⁷ report of illnesses among a general population group, 61 per cent were due to respiratory infection. Holland⁸ found that minor respiratory and acute communicable disease accounted for three-fourths of the illnesses of children aged less than 15 years. Gastrointestinal illnesses were next in frequency and comprised 19.1 per cent of the total number of illnesses. The latter were all cases of quite mild diarrhea and gastroenteritis, and none of the infants required hospital care. Communicable disease caused 4.3 per cent of the illnesses, chickenpox and rubella being the most frequent. Since there was such a small number of communicable diseases the rates cannot be compared with those in Godfrey's,⁹ Holland's,¹⁰ and Collins's¹¹ studies. Roseola infantum was the diagnosis in 2.8 per cent of the illnesses and other diseases accounted for 0.9 per cent.

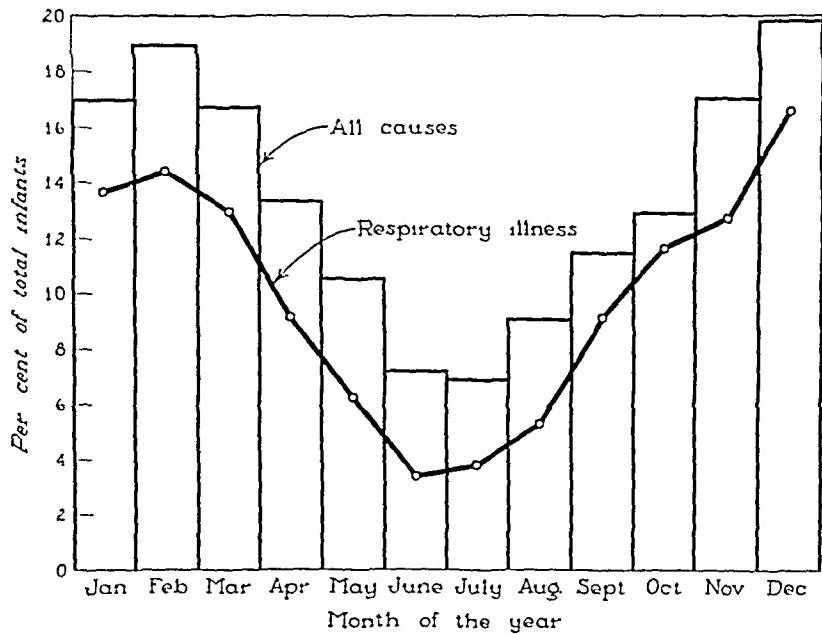


Fig 2.—Seasonal incidence of illness.

A seasonal variation in the incidence of infection was expected and this tendency is clearly shown in Fig 2. The rate of the respiratory illnesses follows closely the frequency of total illnesses throughout the entire year. The peaks for both were in December and February and the lowest levels were in June and July. Since there was no seasonal fluctuation in the rate of the gastrointestinal illnesses in this group of infants, it was not depicted in the graph.

In Grulee and his associates' study¹² the respiratory infections were greatest in the spring and the gastrointestinal disturbances were highest in the summer.

TABLE II. THE DURATION OF BREAST FEEDING IN RELATION TO THE RATE OF ILLNESS

DURATION BREAST FEEDING (MO.)	INFANTS	ILLNESS RATE				TOTAL	
		BIRTH-6 MO.		6-12 MO.			
		ALL CAUSES	RESPIRATORY	ALL CAUSES	RESPIRATORY		
0	55	0.33	0.27	0.83	0.58	1.16	
Less than 3	202	0.49	0.37	1.34	0.98	1.83	
3-5	59	0.37	0.31	1.14	0.73	1.51	
6-8	73	0.32	0.25	1.25	0.88	1.57	
9+	28	0.32	0.25	1.18	0.93	1.50	

Much has been said concerning the influence of breast milk on morbidity in this age period. Grulee and his associates^{5, 6} found lower morbidity and mortality rates among breast-fed and partially breast-fed infants than among the artificially-fed infants. Stevenson found a significant difference between the average number of respiratory infections in breast-fed and in artificially-fed infants but not in the number of gastrointestinal and other infections. However, Stevenson found no significant difference between the number of respiratory infections per infant in the breast-fed and the artificially-fed groups within the first six months of life but he did find a difference in the second six months of life. In Table II it is shown that the duration of breast feeding among the 417 infants did not influence the rate of incidence of all types of illness and respiratory infections per infant within the first year of life. The illness rate for the breast-fed babies (1.69 ± 0.07 per infant) was significantly higher than the rate for those (1.16 ± 0.16 per infant) who were never put to breast at any time. This increased incidence for illness occurs during the second six months of life and is directly opposite to the conclusion reached by Stevenson. Respiratory illness showed a similar pattern. However, many other factors may influence the number of illnesses noted. Ebbs and his associates¹² found that the incidence of illness in babies up to the age of 6 month and the number of deaths resulting from these illnesses were many times greater in the group whose mothers had poor prenatal diets. The supplementary diet of mothers during breast feeding and the diets of the infants, exposure to older children and adults, and housing conditions, are possible factors in the incidence of illness. These factors may obliterate the influence of breast feeding.

SUMMARY

Among 417 infants observed for attacks of illness within their first year of life, the incidence of illness was not influenced by sex.

The incidence of illness was 1.63 per infant per year.

The frequency of illness increased as the infants approached 1 year of age. There was a definite seasonal fluctuation in the incidence of respiratory illnesses but not in the incidence of gastrointestinal illnesses.

Respiratory illnesses comprised nearly 73 per cent of the illnesses during the first year of life.

From a statistical standpoint the duration of breast feeding did not influence the rate of illnesses for the period studied. However, it must be remembered that many other factors predisposing to illness may have obliterated this single influence.

REFERENCES

1. Collins, S. D.: Pub. Health Rep. 63: 637, 1948.
2. Falk, I. S., Klem, Margaret C., and Sinai, Nathan: The Incidence of Illness and the Receipt and Costs of Medical Care Among Representative Families; Experience in Twelve Consecutive Months During 1928-1931, Chicago, 1933, The University of Chicago Press.
3. Sydenstricker, Edgar: Pub. Health Rep. 42: 1565, 1927.
4. Stevenson, S. S.: J. PEDIAT. 31: 616, 1947.
5. Grulce, C. G., Sanford, H. N., and Herron, P. H.: J. A. M. A. 103: 735, 1934.
6. Grulce, C. G., Sanford, H. N., and Schwartz, Harry: J. A. M. A. 104: 1986, 1935.
7. Sydenstricker, Edgar: Pub. Health Rep. 41: 2069, 1926.
8. Holland, Dorothy F.: Pub. Health Rep. 55: 227, 1940.
9. Godfrey, E. S., Jr.: Am. J. Pub. Health 18: 616, 1928.
10. Holland, Dorothy F.: Pub. Health Rep. 55: 135, 1940.
11. Collins, S. D.: Pub. Health Rep. 50: 237, 1935.
12. Grulce, C. G., Sanford, H. N., and Kanter-Amtoman, Jennie: J. PEDIAT. 6: 825, 1935.
13. Ebbs, J. H., Tisdall, F. F., and Scott, W. A.: J. Nutrition 22: 515, 1941.

TREATMENT OF PERTUSSIS WITH POLYMYXIN B (AEROSPORIN)

SEYMOUR KAPLAN, M.D., ALFRED E. FISCHER, M.D., AND JEROME L. KOHN, M.D.
NEW YORK, N. Y.

POLYMYXIN is a new antibiotic which in laboratory studies is active against a wide variety of gram-negative organisms. Benedict and Langlykke¹ first reported the antibiotic properties of crude extracts of *Bacillus polymyxa*. Shortly thereafter Ainsworth and associates² described the chemotherapeutic activity of a relatively pure extract which they derived from *Bacillus aerosporus* and which they called "aerosporin." Stansly and associates³ independently reported on the antibiotic activity of *B. polymyxa* and named the active principle "polymyxin." It was soon found that *B. polymyxa* and *B. aerosporus* were identical organisms and at a recent conference⁴ on antibiotics derived from this bacteria it was decided that all further derivatives would be called polymyxin. Differentiation was to be made by use of lettering such as Polymyxin A, Polymyxin B, etc. Schoenbach and his associates⁵ have continued the experimental and clinical investigations with the polymyxin described by Stansly (designated Polymyxin D). Aerosporin has been further purified and the new antibiotic is known as Polymyxin B. Polymyxins B and D apparently differ not only in biochemical properties but in therapeutic and toxic effects as well.

In a recent publication, Brownlee and Swift^{6, 7} reported their results with the use of aerosporin in the treatment of pertussis, and concluded that this extract had a definite therapeutic value. Toxic effects were noted, but these were transient, and it was felt that they were due to impurities. Because of these suggestive results and with the production of the purified aerosporin product, Polymyxin B, we decided to treat a series of patients with pertussis with this new antibiotic.

METHODS AND MATERIALS

Eighty-four patients with pertussis were treated with Polymyxin B from August to November, 1948, at Willard Parker Hospital, sixty-six by the intramuscular route, and eighteen by aerosol inhalation (Table I). The diagnosis

TABLE I. THE EIGHTY-FOUR INVESTIGATED PATIENTS WITH PERTUSSIS TREATED WITH POLYMYXIN, ACCORDING TO AGE AND METHOD OF TREATMENT

SIXTY-SIX PATIENTS TREATED INTRAMUSCULARLY				
Ages	0-6 mo.	7-12 mo.	1-2 yr.	2 yr. and over
No. of patients	19	10	10	27
EIGHTEEN PATIENTS TREATED BY AEROSOL INHALATION				
Ages	0-6 mo.	7-12 mo.	1-2 yr.	2 yr. and over
No. of patients	3	6	1	7

From the Willard Parker Hospital, Department of Hospitals, New York, N. Y.

This study was aided by a grant from Burroughs Wellcome and Co., Tuckahoe, N. Y., who also supplied Polymyxin B.

*New York Academy of Sciences, Section on Biology, May 21 and 22, 1948

in all cases was substantiated by bacteriologic or hematologic studies in addition to the history and clinical findings. Admission roentgenograms of the chest were taken on all patients, were repeated routinely after treatment, and were taken again whenever clinical signs indicated pulmonic complications.

Because previous workers using polymyxin reported kidney toxicity, daily urinalyses were done on all patients while under treatment and for three days thereafter. Serial nonprotein nitrogen levels were taken during the course of treatment on the first twenty patients.

Polymyxin B was supplied in ampules as a dried, colorless hydrochloride, each ampule containing the equivalent of 40 mg. of polymyxin. A dried sulfate preparation equivalent to 50 mg. of Polymyxin B per ampule was also given to a few patients toward the end of the study. Sterile saline was used as the diluent.

The intramuscular dosage was 0.8 mg. per kilogram of body weight every four hours (4.8 mg. per kilogram per day). This dosage was given for five consecutive days, as previously suggested by Brownlee and Swift.^{4, 5} The hydrochloride solution caused pain about the site of injection in all patients. A sulfate preparation causing less local irritation was used in a few patients. None of the reactions resulted in necrosis.

When the drug was administered by the aerosol method, 60 per cent of the estimated intramuscular dose was divided into four doses: at 9 A.M., 1 P.M., 5 P.M., and 9 P.M. The Vaponephrin plastic nebulizer* was used and saline was added to each individual dose, so that 2 c.c. of fluid containing the polymyxin was always given. The nebulizers were checked so that it always took at least ten to fifteen minutes for each aerosol procedure. After every treatment 1 c.c. of saline was added to the nebulizer to wash out the precipitated drug. In general, about 3 to 4 L. of oxygen per minute provided sufficient vaporization and the desired length of treatment. Infants below 8 months of age were usually placed in plastic hoods for aerosol therapy. For older children cones were made from discarded roentgenographic film, and these cones were placed about the nozzle of the nebulizer with the wide end being held gently over the nose and mouth. Blood levels obtained with both methods of administration indicated good absorption.

Patients with evidence of bronchopneumonia or convulsions were not treated with polymyxin. Since the therapeutic efficacy of this drug had not been proved, it was felt unjustifiable to deny these critically ill patients hyperimmune serum and other therapy. For this reason we could not use alternating controls. We did not feel that selected controls would be of any value because of the difficulty in obtaining two groups of similar age and comparable severity and length of illness.

The patients treated with polymyxin received no other medication except for a few that had been given sulfonamides prior to admission. The general management of the patients was essentially as outlined by the co-authors in a previous publication.⁷

*Vaponephrin Company, Upper Darby, Pennsylvania.

LABORATORY RESULTS⁴

In all patients an attempt was made to isolate *Hemophilus pertussis* organisms. Cultures were taken daily for the first three days after admission, and in twenty-one patients they were also obtained during and after treatment. The nasopharyngeal swab method of taking cultures as described by Bradford⁸ was used. Positive cultures were obtained in thirty-four of the eighty-four patients. More significantly, however, positive cultures were obtained in ten of twenty-one patients in which cultures were taken during and after therapy. In five of these patients the positive growths were from cultures taken on the third to the fifth day of treatment, and in the remaining five from cultures taken two weeks after onset of treatment.

Blood level determinations were done on samples taken three and one-half to four hours after intramuscular injection and one hour after aerosol administration. Twenty-six determinations from the intramuscular group showed an average of 46 units per milliliter of serum (one unit is equal to $\frac{1}{10}$ $\mu\text{g}.$). The range varied between 26 and 70 units with well over one-half in the 26 to 42 range. Thirteen determinations made on patients receiving aerosol therapy averaged 23 units per milliliter of serum with the range from 20 to 26 units per milliliter of serum. We noticed no significant cumulative effect, since levels taken on the first day of treatment were not appreciably different from those which were taken on the third, fourth, and fifth days. This was found to be true whether the drug was given by the intramuscular route or by aerosol. There was no correlation between the blood levels and results of treatment.

Although we used the same dosage as Brownlee and Swift, they obtained levels between 2 and 4 units per milliliter of serum. Their method of determination, however, was different from that used in our laboratory and may explain the lack of similar laboratory results. Two other laboratories,[†] using the same blood specimens with which we made our determinations, confirmed our results on several patients.

Sensitivity studies using Levinthal's media for the *H. pertussis* were done. Serial dilutions of Polymyxin B in saline were inoculated with the test cultures. The results showed that an average of 1.2 units of Polymyxin B were necessary to prevent the growth of *H. pertussis* organisms, a somewhat higher average than that reported by Brownlee.⁶ The significant point, however, is that the blood levels with the dosage used were in all instances many times above the calculated sensitivity range.

Attempts to do the sensitivity tests by the agar cupplate method or by the direct incorporation of Polymyxin B into the Bordet-Gengou media were unsuccessful.

CLINICAL RESULTS

In Tables II and III are listed the results which were graded as improved, failure, or equivocal. A case was considered improved if there was notable im-

⁴Laboratory assistance was given by Arthur Vogel, B.S. Details of laboratory procedure are to be published in a separate report.

[†]Hobby, G. L., Chris Pulzer and Co., Inc., Brooklyn, N. Y.; Laboratory of Burroughs Wellcome and Co., Tuckahoe, N. Y.

provement in the course of the disease within seven days after the onset of treatment. Since polymyxin is a specific bactericidal agent, a discernible change in the course of the disease would be expected within this time. Improvement, as it is observed in patients successfully treated with human hyperimmune serum, occurs within a week after the onset of treatment.⁹⁻¹²

TABLE II. RESULT OF TREATMENT IN SIXTY-SIX PATIENTS RECEIVING INTRAMUSCULAR INJECTIONS ACCORDING TO AGE AND SEVERITY OF ILLNESS AT THE ONSET OF TREATMENT

AGE	CONDITION AT ONSET OF TREATMENT			RESULT OF TREATMENT		
	MILD	MODERATE	SEVERE	IMPROVED	EQUIVOCAL	FAILURE
0-6 mo.	7	4	8	3	2	2
						4
						6
7-12 mo.	2	6	2	1	1	
						6
						2
1-2 yr.	3	4	3	1	2	
						3
						3
2 yr.+	8	19	0	6	2	
						10
Totals						
Mild	20			11	7	2
Moderate		33		10	0	23
Severe			13	2	0	11
Sixty-six patients				23	7	36

TABLE III. RESULT OF TREATMENT IN EIGHTEEN PATIENTS TREATED WITH AEROSOL INHALATION ACCORDING TO AGE AND SEVERITY OF ILLNESS AT ONSET OF TREATMENT

AGE	CONDITION AT ONSET OF TREATMENT			RESULT OF TREATMENT		
	MILD	MODERATE	SEVERE	IMPROVED	EQUIVOCAL	FAILURE
0-6 mo.	2	2	0		2	2
7-12 mo.	2	4	0	1	2	3
1-2 yr.	1	0	0		1	
2 yr.	4	3	0	4		3
Totals						
Mild	9			4	5	0
Moderate		9		1	0	8
Severe			0			
Eighteen patients				5	5	8

Analysis of Table II shows that of the forty-six children who were moderately or severely ill at the onset of treatment, thirty-four failed to show improvement in seven days. It was this group for which specific therapy was needed and in which the most accurate observations as to the efficacy of the treatment could be made. The twelve children in this group who were listed as improved within seven days of the onset of therapy could not all be considered as therapeutic

responses. Six of these children were in the fourth week of illness and may simply have reflected the natural convalescence. Only two of the twelve children were under one year of age, and only two patients showed a really significant change in the course of illness. On the other hand, the thirty-six patients listed as failures showed no alteration in the course of their entire illness.

Since it might be said that the length of therapy was not sufficient to obtain a therapeutic effect, the course of therapy was repeated in two patients who had failed to respond initially. Beneficial results were not noted with the second course of treatment.

The improvement noted among the mildly ill children lost its significance in view of the lack of clear-cut criteria before and after treatment. Most were actually equivocal and may have represented natural convalescence as suggested from similar untreated patients observed during the same period of investigation. Lack of systematic controls prevented any definitive statement in this regard.

The children who received aerosol therapy (Table III) showed the same results as were observed in the patients treated by the intramuscular route. The group was small but the failures were convincing. No severely ill children were treated in this group because of the evident inability to obtain any significant results with the intramuscularly treated group.

Complications developed in fifteen patients. Nine had pulmonary involvement as evidenced by atelectasis, pneumonia, or emphysema, four had diarrhea, and two had otitis media. There were no deaths.

TOXICITY

Swift and Brownlee^{5, 6} reported transient albuminuria in nine of ten patients treated with aerosporin. Laboratory studies on mice indicated the existence of a nephrotoxic factor with the main damage occurring in the tubules. Polymyxin B, the purified aerosporin used in our investigation, was thought to be free of the nephrotoxic factor. However, as shown in Table IV, albuminuria was present in thirty-three of the sixty-six patients treated with the intramuscular polymyxin. It varied from a trace to 3 plus. In most instances this was associated with few to many leucocytes per high power field (centrifuged). The albuminuria and leucocytes were transient in all patients and disappeared after treatment was concluded. Urinalyses done on twenty-one children in the follow-up clinic a month after discharge revealed no evidence of pathology. Serial nonprotein nitrogen levels taken during and after treatment in the first twenty patients showed no elevation. Single nonprotein nitrogen determinations in thirteen other patients revealed no rise above the normal.

TABLE IV. TOXICITY NOTED ACCORDING TO METHOD OF TREATMENT

TOTAL NO. PATIENTS	FEVER	URINARY FINDINGS		LETHARGY, ANOREXIA
		ALBUMIN	LEUCOCYTES	
66 intramuscular	62	33	26	60
18 aerosol	10	2	1	1

Elevation of temperature was present in sixty-two of sixty-four intramuscularly treated patients while on therapy. Elevation was coincident with the onset of therapy and persisted in most patients for as long as one day after treatment.

It was as high as 39° to 40° C. in several instances, with the average between 37° and 38.6° C. In only four children treated by intramuscular therapy did a temperature elevation fail to develop. In general, the elevation was higher in the older children.

Perhaps the most distressing toxic symptoms noted were marked lethargy, irritability, and anorexia. These were present in all but six of the intramuscularly treated patients and were severe enough in some children to necessitate the use of parenteral fluids to maintain hydration and nutrition. These symptoms were noted shortly after treatment was instituted and persisted until therapy was completed. Oliguria, which was noted in several patients, was felt to be secondary to the limited fluid intake induced by anorexia.

As might be expected with the lower blood levels in patients treated by aerosol inhalation, toxicity was less pronounced. One patient who had marked lethargy, anorexia, and irritability had a temperature of 40° C. Slight elevation of temperature was present in nine children, and in one the urine contained leucocytes.

It should be stated that other investigators, using only slightly higher dosages of polymyxin per kilogram of weight, found significant liver damage in dogs.¹³ No jaundice or other clinical evidence of liver toxicity was noted in our patients, but no laboratory studies for hepatic function were done.

DISCUSSION

It is evident from the above results that no dramatic effect on the course of pertussis was noted within seven days of the onset of therapy. The question as to whether or not the duration of illness was shortened by polymyxin therapy is much more difficult to evaluate. There is hardly any therapeutic measure which has not been found by some investigator to shorten the course of pertussis. This arises from the difficulty of determining the normal course of untreated pertussis. It is generally agreed that the disease progresses in severity, reaching its peak about the second week of the paroxysmal stage and then gradually subsiding. Bamberger and Menke,¹⁴ observing 100 untreated patients, plotted the frequency of paroxysms against the days of illness. They established a normal gradient of the decline of the frequency of paroxysms in their patients after the paroxysms had reached a peak. They felt that a therapeutic agent could best be evaluated by comparing the frequency of paroxysms, and particularly the rate of decline of paroxysms, against this norm. Fig. 1 is an illustration of the frequency of paroxysms in fifty-five of sixty-six of our patients treated intramuscularly, where treatment was started by the second or third week of illness. Patients whose treatment was instituted after that time are not included. The daily frequency of paroxysms is the median average per day and is charted against the week of illness. The gradual decline in the frequency of paroxysms as well as the number of paroxysms per day should be noted. The chart follows the pattern observed by Bamberger and Menke in their untreated patients. Other investigators using this method of analysis have found similar results in their ineffectually treated and control patients.¹⁵⁻¹⁷ It is, of course, hazardous to compare one group of pertussis patients with another when all the variables are not taken into consideration. The only point which we wish to illustrate by this

graph, however, is the failure of any decided change in the occurrence of the frequency of paroxysms during the seven-day period after treatment, as noted previously, or in the declining phase of the disease. While it would be fallacious to use the comparison of one factor (frequency of paroxysms) as the one basis of evaluation, it offers a reliable index of the general over-all picture. Consideration of the other factors, such as nutrition and the general condition of the patient and the development of complications, substantiated this observation. The patients gained weight slowly, emesis persisted with the continuance of the paroxysms, and hospitalization was prolonged. As noted above, complications developed in fifteen patients.

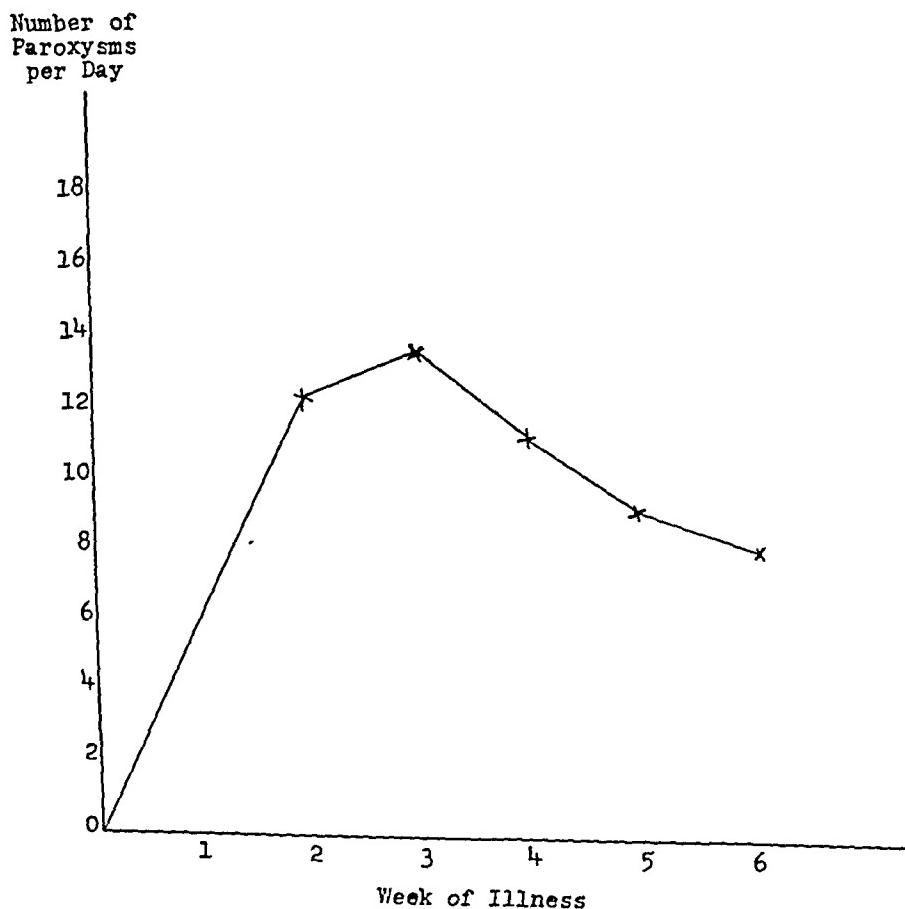


Fig. 1.—The daily frequency of paroxysms during successive weeks and illness in fifty-five patients receiving intramuscular therapy.

The roentgenologic findings were often not correlated with the clinical picture. Radiodensity of the entire right middle lobe was present without fever or malaise in one child. On the other hand, sibilant and crepitant râles with fever were often present with completely negative roentgenograms. The most significant findings were atelectasis and emphysema. This is mentioned because

the diagnosis of bronchopneumonia was frequently made prior to admission and was often not corroborated by the clinical or laboratory findings.

No deaths occurred during the period of investigation. This, however, is no reflection on the efficacy of polymyxin therapy, since the critically ill children were not included in the investigation. However, it should be mentioned that the mortality rate from pertussis has markedly decreased in recent years.^{18, 19} This was evident even before the use of specific therapy and should be taken into consideration when treatment is evaluated on the basis of differences in mortality rates.

Our results, then, fail to show any significant therapeutic effect of polymyxin therapy on the course of pertussis when treatment is started during the second and third week of illness. Certainly the consistent toxic effects observed would militate against its usefulness during this stage of the disease. It is impossible for us to say whether the therapy would be more effective if instituted during the catarrhal or early paroxysmal stage. Two of the six children who were treated during this early phase of the disease went on to develop moderate and severe symptoms. These are too few patients for any conclusion to be drawn. Since there is no way of foretelling the natural progress of the disease, it must be remembered that any therapy started prior to the peak of illness cannot be evaluated by the subsequent course of the disease unless a statistically significant group is considered.

The bacteriologic findings of *H. pertussis* organisms in the nasopharynx after a course of therapy is sufficient evidence of the failure of the drug to eradicate the invading organisms. The slightly inhibiting effect of serum on polymyxin activity of in vitro studies⁵ is suggestive of greater inhibition by human humoral factors. The laboratory failure to identify polymyxin biologically in urine, bile, and cerebrospinal fluid⁶ is further evidence suggesting humoral and particularly tissue inactivation of the drug.

The possibility that insufficient concentration of the drug might reach the bronchial tissues through the blood stream brought about the trial of aerosol therapy. The results were no more encouraging.

Although Swift⁴ concluded that aerosporin was of definite therapeutic value in the treatment of pertussis, an analysis of his results is not impressive. Only ten patients were reported, with two deaths. In view of our results with Polymyxin B, we are unable to corroborate his conclusions.

CONCLUSIONS

1. Polymyxin B, when given during the second or third week of pertussis, had no significant effect either within seven days after the onset of therapy or on the over-all disease process. There is no indication that, were treatment started during the first week, better results would have been obtained; two of six patients treated very early developed moderate to severe whooping cough.

2. Toxic effects were noted in all patients treated with intramuscular injections of Polymyxin B. Severe toxic symptoms appeared in only one patient treated by aerosol inhalation. Toxicity was manifested by fever, albumin and

cellular elements in the urine, and by lethargy, irritability, and anorexia. In all instances, the toxic symptoms and signs were transient and subsided with the discontinuance of treatment.

3. Blood levels in all determinations were many times above the sensitivity range for polymyxin on *H. pertussis* organisms obtained from patients.

4. We are unable to explain the failure to obtain favorable clinical results, despite the encouraging laboratory findings of in vitro and in vivo studies.

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REFERENCES

1. Benedict, R. G., and Langlykke, A. F.: Antibiotic Activity of *Bacillus Polymyxxa*, *J. Bact.* 54: 24, 1947.
2. Ainsworth, G. C., Brown, A., and Brownlee, G.: "Aerosporin," An Antibiotic Produced by *Bacillus Aerosporus Greer*, *Nature, Lond.* 160: 263, 1947.
3. Stansly, P. G., Shepherd, R. G., and White, H. G.: Polymyxin: A New Chemotherapeutic Agent, *Bull. Johns Hopkins Hosp.* 81: 43, 1947.
4. Schoenbach, E. B., Bryer, M. S., Bliss, E. A., and Long, P. A.: Polymyxin: Note on Experimental and Clinical Investigations, *J. A. M. A.* 136: 1098, 1948.
5. Swift, P. N.: Treatment of Pertussis With Aerosporin, *Lancet* 1: 133, 1948.
6. Brownlee, G., and Bushby, S. R. M.: Chemotherapy and Pharmacology of Aerosporin, *Lancet* 1: 127, 1948.
7. Kohn, J. L., and Fischer, A. E.: Management of Whooping Cough With Special Reference to Infants, *Am. J. Dis. Child.* 73: 663, 1947.
8. Bradford, W. L., and Slavin, B.: Nasopharyngeal Cultures in Pertussis, *Proc. Soc. Exper. Biol. & Med.* 43: 590, 1940.
9. McGuinness, A., Armstrong, J., and Felton, H.: Hyperimmune Whooping Cough Serum, *J. PEDIAT.* 24: 249, 1944.
10. Kohn, J. L., Rudel, G., Weichsel, M., and others: Hyperimmune Serum in Treatment of Whooping Cough, *Am. J. Dis. Child.* 74: 321, 1947.
11. Scheinblum, I., and Bullowa, J.: Treatment of Pertussis With Lyophile Hyperimmune Human Pertussis Serum, *J. PEDIAT.* 25: 49, 1944.
12. Lapin, J.: Serum in the Prophylaxis of Contacts and the Treatment of Whooping Cough, *J. PEDIAT.* 26: 555, 1945.
13. Werner, C. A.: Personal communication.
14. Bamberger, P., and Menke, H.: Der Normalverlauf der Keuchhustenerkrankung als Maßzstat zur Beurteilung von Heilversuchen, *Klin. Wechschr.* 14: 1036, 1935.
15. Cohen, P., Weichsel, M., and Lapin, J. H.: A Comparative Study of Therapeutic Agents in the Treatment of Pertussis, *J. PEDIAT.* 16: 30, 1940.
16. Lapin, J. H.: Whooping Cough, Springfield, 1943, Charles C Thomas, pp. 183-190.
17. Faber, H. K., and Struble, H. P.: Does Roentgen Ray Modify the Course of Whooping Cough? *J. A. M. A.* 85: 815, 1925.
18. Stimson, P. M.: A Manual of the Common Contagious Diseases, Philadelphia, 1947, Lea and Febiger, p. 233.
19. Marks, H. H., Kohn, J. L., and Fischer, A. E.: A Countrywide Survey of Pertussis Morbidity and Mortality. To be published.

THE TREATMENT OF THE ANGINOSE TYPE OF INFECTIOUS MONONUCLEOSIS WITH GAMMA GLOBULIN

ALBERT G. BOWER, M.D., JOHN E. AFFELDT, M.D., AND HAROLD WEST, M.D.

PATIENTS with infectious mononucleosis enter the hospital with diagnoses of typhoid fever, Vincent's angina, and, most frequently, diphtheria.

Ordinarily, infectious mononucleosis requires little more than supportive care and a watchful eye by way of therapy, but it occasionally appears in severe forms and may terminate fatally.

Cases of the anginose type are characterized by severe membranous tonsillo-pharyngitis and it may not be possible to differentiate the membrane from that of diphtheria except by laboratory means. Generalized adenopathy and splenomegaly are usually likewise present and aid in establishing the correct diagnosis. However, the final and conclusive evidence comes from the laboratory in the form of a lymphocytosis in the differential blood count, the typical vacuolated Downey cell being present and diagnostic. The heterophile test is rarely positive before the twelfth day, so it is of little early assistance in diagnosis, but the absence of Klebs-Loeffler bacilli in the throat smears and culture is significant. Vincent's organisms are often present and may mislead the inexperienced. When the patients have first received any type of therapeutic serum, the heterophile test must be corrected by absorption.

The use of human pooled convalescent scarlet fever serum in the treatment of infectious mononucleosis was first reported by Berkley.¹ Its successful employment in our hands led us to attempt its replacement as a therapeutic agent with human gamma globulin, as we felt that the gamma globulin content of the original scarlet fever serum treatment might be the factor responsible for its beneficial result.

We use gamma globulin in doses of 4 to 8 ml. intramuscularly and one dose usually suffices. No untoward reactions have occurred.

Penicillin is also given, and occasionally sulfonamides to take care of secondary invaders, but their use alone does not favorably influence the course of the disease. Because of mistaken diagnosis or the difficulty in establishing a correct diagnosis early in the disease, 20,000 to 60,000 units of diphtheria antitoxin frequently have been given before any other therapeutic procedure. This in itself does not favorably alter the course of the disease. In this connection the disease may be startling in its resemblance to septic diphtheria: the extensive membrane and edema force the consideration of tracheotomy though careful search fails to disclose the typical vacuolated Downey cells, diphtheroids being present in smears, and no report on throat culture being available for twelve to twenty-four hours. It is because of this uncertainty in diagnosis and

From the Department of Public Health and Preventive Medicine of the College of Medical Evangelists, and the Communicable Disease Section of the Los Angeles County General Hospital.

TABLE I. DIAGNOSIS, TREATMENT, AND RESULTS IN INFECTIOUS MONONUCLEOSIS

CASE NO.	AGE IN YEARS	IMMUNOGLOBULIN TITERS	PENICILLIN (DOSE, D.V.T.)	GAMMA GLOBULIN (DOSE, RATE)	DATE OF IMPROVEMENT OCCURRED	NO. DAYS AFTER NO. DAYS AFTER	
						GLOBULIN IMPROVEMENT OCCURRED	PENICILLIN IMPROVEMENT OCCURRED
1	16	112	-	50,000 U. 1/5 \bar{q} 3 h.	4/8	4/9	1
2	21	118	60,000	50,000 U. 4/8 \bar{q} 3 h.	6 e.c.	4/5	1
3	17	119	-	40,000 U. 4/5 \bar{q} 2 h.	8 e.c.	4/6	1
4	6	112	60,000	40,000 U. 1/23 \bar{q} 3 h.	13 e.c. 1/23	1/26	3
5	8	56	-	100,000 U. 2/14 \bar{q} 3 h.	6 e.c. 2/17	2/20	3
6	21	56	-	20,000 U. 4/15 \bar{q} 3 h.	5 e.c. 4/15	4/16	1
7	7	224	10,000	40,000 U. 10/30 \bar{q} 3 h.	8 e.c. 10/31	11/2	3
8	6	224	-	40,000 U. 1/9 \bar{q} 3 h.	10 e.c. 1/9	1/10	1
9	7	112	-	50,000 U. 1/4 \bar{q} 3 h.	8 e.c. 1/4	1/8	4
							1/6 100 c.c. immune serum I.V. 1/6 Tracheotomy
10	16	112	10,000	60,000 U. 10/1 \bar{q} 3 h.	6 e.c. 10/4	10/5	1
11	11	224	10,000	50,000 U. 10/25 \bar{q} 1 h.	8 e.c. 10/31	11/1	4
12	3	224	-	20,000 U. 4/8 \bar{q} 3 h.	8 e.c. 4/12	4/13	7
13	4	112	60,000	40,000 U. 3/3 \bar{q} 3 h.	5 e.c. 3/4	3/6	5
14	6	224	-	30,000 U. 3/3 \bar{q} 3 h.	10 e.c. 3/3	3/4	3
							1/6 100 c.c. immune serum I.V. 1/6 Tracheotomy

the known danger of withholding diphtheria antitoxin for even a few hours in such cases, should they prove to be clinical diphtheria, that antitoxin in full therapeutic dosage often is so given.

Table I shows the course of fourteen cases selected from among those treated in 1947. All were clinical cases of anginose type of infectious mononucleosis and had heterophile agglutination titers after absorption of 1:56 or higher by the Paul and Bunnell² method. All received gamma globulin and were the severe cases to which we have restricted this type of therapy.

CASE REPORTS

CASE 11.—A 14-year-old white girl admitted Oct. 27, 1947 had been ill six days with sore throat and fever of 101° F. On the third day of illness she was given penicillin and sulfonamides. When no response to therapy was noted and a membrane on the throat developed, she was sent to the hospital to rule out diphtheria.

Physical Findings.—Temperature was 103° F. A moderately severe pharyngitis with a dirty grey membrane on both tonsils and generalized adenopathy were present. The spleen was not palpable, but dullness was percussible to the seventh rib in the midaxillary line.

Laboratory Examination.—White blood count was 15,000; with 60 per cent lymphocytes, Downey cells being present; heterophile was 1:224 after absorption; throat culture and Wassermann were negative.

Therapy.—On Oct. 27, 1947, the day of admission, 40,000 units of diphtheria antitoxin were given, and 50,000 units penicillin every three hours; October 31, 8 ml. gamma globulin were given intramuscularly. For three days after admission temperature ran to 103° F. and membrane became worse (six days after beginning penicillin). On November 1, the temperature dropped. On November 2 the membrane disappeared. She was discharged Nov. 6, 1947.

CASE 12.—Admitted April 11, 1948, a 3-year-old white girl had been ill five days with fever of 102° F., stuffy nose, puffiness about the eyes, and sore throat. Penicillin was started two days after onset; she was sent to the hospital on the third day to rule out diphtheria because of increasing tonsillar exudate.

Physical Findings., moderately severe pharyngitis, bilateral tonsillitis with thick yellowish-grey membrane, generalized adenopathy, a palpable liver, and a questionably palpable spleen were noted. Her temperature was 102° F.

Laboratory Examination.—White blood count was 32,000; mononuclear cells were 85 per cent with many Downey cells present; hemoglobin was 13 Gm.; heterophile was 1:224. Throat culture was negative for diphtheria.

Therapy.—April 11, 1948, penicillin, 20,000 units every three hours intramuscularly, was given. On April 12 gamma globulin 8 ml. intramuscularly was administered: Temperature dropped to normal and throat exudate disappeared on April 13. The patient was discharged April 15.

CASE 9.—Admitted Jan. 14, 1948, a 2-year-old Negro boy had been ill seven days with fever and three days with sore throat, with slight respiratory distress.

Physical Findings.—Temperature was 102° F.; severe pharyngitis with yellowish exudate over both tonsils and generalized adenopathy were present; the spleen was enlarged 3 fingerbreadths to palpation.

Laboratory Examination.—White blood count was 17,500 with 68 per cent mononuclears, many being atypical; throat culture was negative for diphtheria; heterophile was 1:112 after absorption.

Course and Therapy.—On Jan. 4, 1948, 8 ml. gamma globulin and 50,000 units of penicillin were given every three hours intramuscularly; on Jan. 5, 1948, respiratory distress was increasing. Tracheotomy, at first deferred, was done on January 6 because of respiratory retraction, and 100 ml. of human immune convalescent scarlet fever serum were given intravenously. The patient was much improved on Jan. 8, 1948, and the tracheotomy tube was temporarily shut off several times. The tube was removed January 12 and the patient was discharged January 18.

It is interesting to note that Cases 4 and 13 had positive cultures for diphtheria. They were proved to be avirulent strains, however, and not causing disease. There was no question that the correct diagnosis was infectious mononucleosis.

DISCUSSION

Response to gamma globulin is shown in one or more of the following three ways: drop in temperature; disappearance or definite shrinking of the membrane or exudate; general clinical improvement, the latter being distinct from the other two and, at times, actually so dramatic that one confidently expects the patient's rapid recovery.

In this series, therapeutic response appeared within twenty-four to seventy-two hours with one exception (Case 9), and the majority of cases showed all three types of improvement simultaneously. When all three did not occur, the first response noted was the general clinical improvement with a sense of euphoria. This one we consider the most important, for it indicates that the unfavorable course of the disease has changed and recovery has started, and the temperature will drop and the throat improve in the ensuing twenty-four to forty-eight hours. These factors specifically governed selection of the date of improvement designated in the table.

Can the therapeutic response obtained in these cases have been due to the other modalities such as the diphtheria antitoxin or the penicillin? We think not. Many cases have been treated with antitoxin alone in the past, with no effect. Of this series, six received antitoxin first, and their response is no different from those that did not.

Joyce¹ has reported penicillin to be of value in the tonsillopharyngitis of infectious mononucleosis, stating that three out of four cases so treated respond with a drop in temperature within twelve to twenty-four hours. Our experience in those treated with penicillin alone generally has not shown this.

However, in this series of those receiving penicillin, five improved within twenty-four hours and seven within seventy-two hours. In contrast to this, the favorable response to gamma globulin was as follows: eight within twenty-four hours, ten within forty-eight hours, and thirteen within seventy-two hours.

By comparison, a better therapeutic response to gamma globulin is clearly indicated, penicillin showing 50 per cent improvement within seventy-two hours of administration, the severest cases showing nothing noteworthy; whereas with gamma globulin 93 per cent were improved within seventy-two hours.

The mode of action of gamma globulin remains unknown. We do not wish to minimize the effect of penicillin in these cases, but it is our belief that it acts solely upon secondary invaders while gamma globulin is turning the tide. Alone, it is rarely efficacious. Thus the combination may be better than either alone.

We believe gamma globulin should be tried in other forms of severe infectious mononucleosis, such as those with jaundice. It may also speed milder cases to recovery.

SUMMARY

1. Gamma globulin, 4 to 8 ml. intramuscularly, was used therapeutically for severe cases of infectious mononucleosis, anginose type.
2. Fourteen cases were reviewed; all had anginose type, had a heterophile agglutination of 1:56 or higher, and all received gamma globulin and penicillin.
3. Statistical evidence is in favor of gamma globulin over penicillin as the major therapeutic factor.
4. Trial on milder cases and other types of infectious mononucleosis is advocated.

REFERENCES

1. Berkley, H. K.: *J. PEDIAT.* 20: 26, 1942.
2. Paul, J. R., and Bunnell, W. W.: *Am. J. M. Sc.* 183: 99, 1932.
3. Stuart, C. A., Welch, H., Cunningham, J., and Burgess, A. M.: *Arch. Int. Med.* 58: 512, 1936.
4. Joyce, F. T.: *Arch. Int. Med.* 78: 49, 1946.

TRACHEAL TUMORS IN INFANTS AND CHILDREN

JOSEPH G. GILBERT, M.D., F.A.C.S., BENJAMIN KAUFMAN, M.D., F.A.A.P., AND
LAURENCE A. MAZZARELLA, M.D., F.A.C.S.
BROOKLYN, N. Y.

TUMORS having their origin in the trachea are of rare occurrence in infants and children. A review of the literature fails to disclose any reference dealing exclusively with this subject. Textbooks such as *Abt's Pediatrics*,¹ *Brennemann's Practice of Pediatrics*,² *Holt's Diseases of Infancy and Childhood*,³ and *Mitchell-Nelson Textbook of Pediatrics*,⁴ omit mention of this condition.

We are reporting our experience with two cases along with a review of available references to such cases.

Incidence.—From the literature thirty-nine cases of tracheal tumors in infants and children were collected (exclusive of our two cases), making a total of forty-one in all. Our compilation revealed 488 instances in adults.

Pathology.—In infants and children the papillomas are most frequent (56 per cent), followed by fibromas (21.9 per cent). Angiomatous tumors were third (9.7 per cent). (Our two cases were of an angiomatous character.) There were but three cases of malignancy reported. All were of a sarcomatous nature and all occurred in infant females. This is in marked contrast with tracheal tumors in the adult. The following facts appear significant: (1) The incidence of malignancy in adults is about 40 per cent, whereas in infants it is about 7½ per cent. (2) The predominant type of malignancy in adults is carcinoma (about 30 per cent), whereas in infants and children it is sarcoma. (3) Of the benign tumors in the adult, the osteochondromas were most common (15 per cent), followed by papillomas (8 per cent) and fibromas (6 per cent). In infants the highest incidence is that of the papillomas (about 56 per cent) followed by fibromas (22 per cent). (4) Only two cases of angiomas have been reported in the adult. In infants and children it occurred in about 10 per cent.

Site.—The most frequent site of the tumor in the adult has been the lower third of the trachea, followed by the upper third; and least common is the middle third. From the meager information available it appears that the most frequent site in infants and children is the upper third, the inferior third being a poor second.

Symptomatology.—This depends on (1) site of the tumor, (2) type of attachment, and (3) size of the tumor and width of the trachea.

Position.—Tumors arising in the lower third of the trachea growing down into either bronchi gives rise to signs of partial or complete atelectasis in addition to wheezing or harsh breath sounds. If located in the upper third, interfering with the action of the vocal cords, noisy respirations and difficulty in breathing will ensue. Tumors in the middle third are less likely to give rise to severe symptoms and may go unrecognized.

From the Kingston Avenue Hospital for Contagious Diseases. Read in part before the clinicopathologic conference on Jan. 6, 1949.

Type of Attachment.—If the tumor is attached by a pedicle such as in one of our cases, it will ascend on expiration and descend on inspiration. Pedunculated tumors in the lower third, might plug a bronchus during inspiration and give rise to atelectasis, whereas on expiration they might give rise to fewer symptoms. A similar type of attachment in the upper third of the trachea may give rise to very few symptoms during inspiration but to more on expiration. If the attachment is by a broad base the symptoms will be milder, in general, as in the second case.

Size of Tumor and Width of Trachea.—Obviously, the larger the tumor the more the airway is compromised, and the more prominent the symptoms. In the wider trachea of adults one can have a fair-sized tumor with few symptoms. In a recent experience* a 76-year-old woman with a tracheal endothelioma measuring 1 by 0.5 cm., attached by a small pedicle to the posterior wall of the lower third of the trachea, had no signs or symptoms referable to the trachea. This was discovered while performing a diagnostic bronchoscopy.

Differential Diagnosis.—Tracheal tumors in infants and children giving rise to brassy cough, dyspnea, and inspiratory and expiratory difficulties, accompanied with supra- and infrasternal retractions, must be differentiated from laryngismus stridulus, cysts, and papillomas of the larynx.

In laryngismus stridulus there is a crowing inspiratory difficulty starting suddenly, subsiding quickly and spontaneously, and usually occurring during the nocturnal periods. This is of a recurrent character. Laryngoscopy fails to reveal more than an excessive inpulling of the epiglottis and the aryepiglottic folds during inspiration. As the infant grows older, the attacks occur less frequently and less violently and finally subside.

Cysts of the larynx in infants and children are not uncommon and are far more common than tracheal tumors. They arise most frequently from the margins of the epiglottis and aryepiglottic folds. Hoarseness and respiratory difficulty may be present, depending on the size of the cyst and whether it is single, multiple, or pedunculated. Dyspnea is usually made worse during the act of suckling. The diagnosis is made by direct laryngoscopy. Treatment consists in the cysts' removal by use of forceps.

Papillomas of the larynx are more frequently seen than either of the two previously mentioned conditions and usually occur in females. Their most common site is on the vocal cords and less commonly on the false cords. Frequently they grow down into the trachea. (In our consideration of tracheal tumors, we have included only those that had their primary origin in the trachea and have not included papillomas which arose in the larynx and subsequently grew down into the trachea.) Characteristically, papillomas of the larynx appear in bunches, and, after repeated attempts at removal, have a tendency to recur. They tend to disappear spontaneously at about the age of puberty. This is not characteristic of papillomas of the trachea, which either remain stationary in size or start to grow in adult life, possibly becoming malignant. The symptoms of papillomas of the larynx are primarily those of hoarseness and dyspnea. Removal of laryn-

*From the Sea View Hospital Otolaryngological service of Dr. Gilbert.

geal papillomas does not result in a cure, and recurrences are constant. Tracheotomy may be necessary at times in order to give the patient sufficient airway.

Institutions maintaining a "croup service," such as that at our hospital, might have infants with tracheal tumors admitted to such a service without the tumor's presence being suspected. There are several reasons for this. From birth these children have noisy breathing. The significance of this goes unrecognized because the parents accept the noisy breathing as a normal thing and do not seek medical advice (as occurred in our two cases). However, if these children are laryngoscoped, but bronchoscopy is omitted, the cause for the noisy breathing goes undisclosed. They may then be led to believe that the infant will outgrow the noisy breathing. The child may get along fairly well until an upper respiratory infection involves the mucosa of the subglottic and tracheal area and the tumor itself. The swollen tracheal tumor now becomes an obstructive medium and gives rise to more symptoms than would ordinarily have occurred with a simple tracheitis. Suprasternal and infrasternal retractions make their appearance, associated with inspiratory difficulty. Under these circumstances the diagnosis of "croup" is readily and properly made without recognizing the presence of the tracheal tumor. Endoscopy discloses its presence. In our first case an infant child with a tracheal tumor having noisy respiration since birth developed a retropharyngeal abscess which gave rise to severe respiratory difficulty. The child was admitted in extremis with a diagnosis of "croup." Our second case with noisy breathing from birth developed an upper respiratory infection producing classical signs and symptoms of "croup."

One clinical phenomenon common to both was that attempts to gradually narrow the lumen of the tracheotomy tube in preparation for decannulation were time-consuming and extremely difficult (first case, two weeks; second case, three weeks). Furthermore, after decannulation, symptoms of noisy respiration and slight dyspnea still remained in both instances. It was not until further instrumentation disclosed the presence of the tracheal tumor and its removal that the patients were relieved of their symptoms.

CASE REPORTS

CASE 1.—E. S. On Nov. 1, 1948, an 11-month-old white male child was transferred from Kings County Hospital. He had been admitted to Kings County on Oct. 29, 1948, with a two-day history of fever and difficulty in breathing. A diagnosis of mild laryngotracheobronchitis was made there and he was placed on penicillin and sulfadiazine therapy. The child's temperature fell from 103° to 99° F. but he became markedly "croupy" and cyanotic. On admission to Kingston Avenue Hospital, he was breathing with difficulty with marked suprasternal, infrasternal, and epigastric retractions, and was very restless.

On digital examination of the pharynx and hypopharynx no obstruction was palpated. Inspection of the throat revealed moderately enlarged tonsils. Laryngoscopy revealed a markedly injected larynx, the cords moving freely. The tracheal mucosa was found to be irregularly raised and injected and in places covered with tenacious mucus. (The tumor was not recognized at this time because of the inflammatory reaction and mucus covering the tracheal wall.) The bronchi were clear. No foreign bodies were encountered.

As the child grew progressively worse, tracheotomy was performed on the date of admission.

On November 10, decannulation was attempted and because of return of obstructive signs of breathing reecannulation was necessary. Decannulation was successfully accomplished on November 14.

On November 30, because of persistent slight stridor and noisy respirations, a 3.5 mm. bronchoscope was passed through a laryngoscope. The larynx was normal. At a point almost 3 cm. below the level of the cords (below the lowest end of the tracheal incision), a pedunculated, edematous mass attached to the anterior wall, moving downward on inspiration and upward on expiration, was seen. It compromised a little more than one-third of the lumen of the trachea at this site. Using a small foreign-body forceps, the tumor was removed with some difficulty. It was firm with a smooth mucosa and measured 0.3 by 0.2 by 0.2 cm. At the time of its removal it was considered to be a fibroma and it was felt that the tumor's presence explained the noisy respiration present almost from the time of birth.

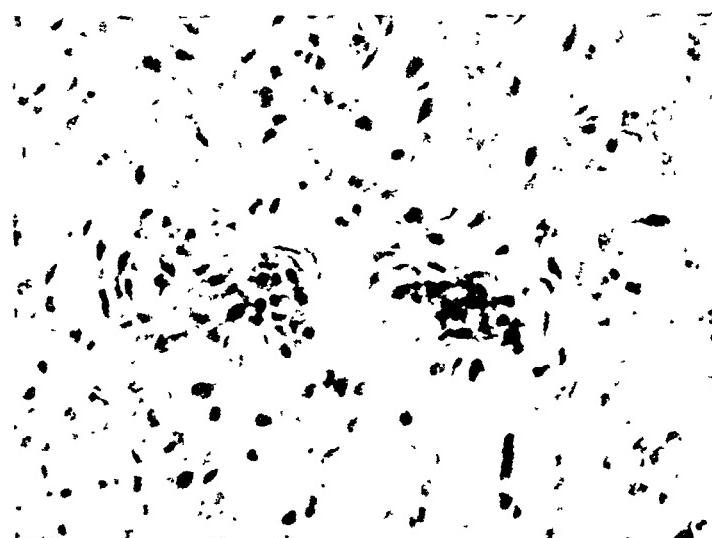


Fig. 1.—Tracheal tumor biopsy of Case 1 (hematoxylin and eosin $\times 450$). Note the vascular spaces containing red blood cells.

The following pathologic report was made by Dr. Rosenblatt:

Gross.—The specimen is a small piece of oval-shaped tissue removed from the trachea.

Microscopic.—The nodule is composed of a loose stroma of fibrous connective tissue which supports numerous small channels lined by a single layer of well-preserved endothelial cells. No muscular wall can be distinguished, but in many instances there is a well-defined, broad band of pink-staining hyaline material. Some of the vascular spaces contain blood. Occasional small lymphocytes are seen within the stroma.

Diagnosis.—Capillary hemangioma of the tracheal wall."

The child's condition improved, and he was discharged on Dec. 12, 1948, in good condition. A re-examination on Jan. 21, 1949, showed him to be in excellent health; he had completely lost his noisy respiration.

CASE 2.—P. L., an 11-month-old Negro female infant, was admitted to Kingston Avenue Hospital on May 28, 1946, in extremis with a history of a progressively increasing cough and dyspnea. The severity of her condition required emergency tracheotomy in the admitting room followed by intracardiac administration of adrenalin and artificial respiration. Following the tracheotomy, a golf-ball-sized mass was seen in the right side of the throat; it was incised and a quantity of foul-smelling pus was evacuated. The child's course in the hospital was febrile and stormy. Despite penicillin therapy, the abscess required incision and dilatation twice, and the child developed bronchial pneumonia. The pneumonia responded well to treatment, being aided by a transfusion of whole blood.



Fig. 2.—Tracheal tumor biopsy of Case 2. *A*, Hematoxylin and eosin stain, $\times 150$. Note round cell infiltration with red blood cells ex-
travasated into connective tissue stroma.

A roentgenogram of the chest showed no evidence of tuberculosis but bilateral bronchopneumonia. A roentgenogram of the cervical area showed only soft tissue swelling.

The child's condition and weight gradually improved with forced feeding and a reinforced diet. The breathing became easier. The mass in the throat subsided. The tracheotomy tube was removed on June 19 and the child remained comfortable. On July 4, the date of discharge, she was fairly well except for some noisy respirations.

On July 30, 1946, the child was readmitted with difficulty in breathing, hoarseness, stridor, and a brassy cry of one week's duration. She had been receiving diphtheria toxoid at the Department of Health station. The last injection was received on July 29. Examination showed her to be afebrile. The tracheotomy scar was well healed. She had a brassy cough, a hoarse cry, no retractions, and was breathing somewhat rapidly. The throat was red and the tonsils large. The pharynx was poorly visualized. A large amount of mucus was coughed up. The impression was that of nondiphtheritic "croup."



Fig. 3.—Lateral view of the neck, showing spherical density directly overlying the trachea at approximately the level of the seventh cervical vertebra. The possibility of foreign body or tumor should be considered.

Inspiratory croup continued, while epigastric intercostal retractions were becoming marked. On August 13 the child had a period of apnea following apparent regurgitation of her formula. She responded well to artificial respiration, oxygen, and suction. The child continued to have noisy respirations and some tugging and retraction of the sternum. She was put in the Trendelenberg position and given penicillin. A roentgenogram on August 15 showed the larynx and trachea to be displaced anteriorly by a retropharyngeal swelling. There was a small, round area of density in the trachea at the level of the seventh cervical vertebra.

On August 21 the child had marked retractions. A roentgenogram that day reaffirmed the presence of a small, dense mass. The possibility of a foreign body was considered. The temperature, pulse, and respiration were normal. Bronchoscopy was performed. The vocal cords appeared normal and moved freely. No obstruction in the larynx was found. In the anterior wall of trachea

at the level of the seventh cervical vertebra there was a small, flapping tumor covered by mucous membrane. Two pieces were removed and sent to the laboratory. The following pathologic report was made.

"*Gross*.—The specimen consists of two fragments of tissue. One fragment measures $0.3 \times 0.2 \times 0.1$ cm. and is brownish-black in color. The other is gray and measures $0.6 \times 0.3 \times 0.2$ cm.

"*Microscopic*.—One fragment is composed of loose, cellular, fibrous, connective tissue stroma, in which there are numerous endothelial-lined channels. The lining cells are occasionally swollen. The stroma is sparsely infiltrated with round cells. Attached to one surface is pink-staining fibrinous material. The other preparation is composed of dense, fibrous stroma, the fibers of which are separated from one another by extravasations of blood. The surface is denuded of lining cells, but attached to it is a fibrinous exudate similar to that described above.

"*Diagnosis*.—Fibroangiomatous polyp of the trachea.

Subsequent roentgenograms showed the absence of the dense mass previously seen. The retropharyngeal space gradually decreased to normal size. The child was discharged on Sept. 4, 1946, in good condition, with no more noisy respiration.

SUMMARY AND CONCLUSION

Two cases of primary tracheal tumors occurring in infants are reported. A survey of the literature and standard textbooks of pediatrics failed to disclose a single article dealing exclusively with this subject. A compilation of data dealing with tracheal tumors occurring in infants and children has been made, disclosing thirty-nine such cases exclusive of the authors' cases. The incidence and the types of tumors encountered is noted and compared with that of the adult. A discussion of the symptomatology and differential diagnosis is included.

REFERENCES

1. Abt's Pediatrics (by various authors), Philadelphia and London, 1926, W. B. Saunders Company.
2. Brennemann's Practice of Pediatrics (by various authors), Hagerstown, Md., 1945, W. F. Prior Co., Inc.
3. Holt, L. E., Jr., and McIntosh, R.: Holt's Diseases of Infancy and Childhood, ed. 11, New York and London, 1946, Appleton-Century-Crofts, Inc.
4. Mitchel-Nelson: Textbook of Pediatrics, ed. 4, edited by Waldo E. Nelson, M.D., Philadelphia and London, 1945, W. B. Saunders Company.
5. Von Bruns, P.: Neubildungen in der Lufttröhre, Handbuch für Laryngologie 1: 952, 1898.
6. Elsberg: Primary Tumor of the Trachea, N. Y. Med. Record, Dec. 1, 883, 1906.
7. Krieg, E.: Ueber die primären Tumoren der Trachea, Beitr. z. klin. Chir. 58: 162, 1908.
8. McKenzie, J.: Referred to by Sauer, Laryngoscope 18: 257, 1908.
9. Sauer, W. E.: Fibroma de Trachea, Laryngoscope 18: 257, 1908.
10. Beco: Papillomes de la Trachee, Annales des Maladies de L'Oreille, 506-7, 1908-1909.
11. Yankauers, S.: Tumor in Trachea, Ann. Otol., p. 418, 1911.
12. Horgan, J. B.: Fibroma of Trachea, Brit. M. J. 2: 652, 1918.
13. Dundas-Grant, J., and Perkins, J. J.: Case of Papillomata of the Trachea, Proc. Roy. Soc. Med. (Sect. Laryng.) 16: 7, 1922-1923.
14. Watkins-Williams, E.: Sarcoma of the Trachea, Proc. Roy. Soc. Med. (Sect. Laryng.) 24: 1637-1638, 1930-1931.
15. Richards, L. G., and Dietrich, H. F.: Fibrosarcoma of the Trachea, Ann. Otorhinolaryngol. 43: 892-905, 1934.
16. Abbatte, L.: Sarcome de la Trachee, Archiv für Ohrenheilkunde 140: 179, 1936.
17. Baldenweck, L., and Pouquet: Fibrome de la Trachee, Bronchoscop., oesophagoscop. et gastrop. 2628: 213-218, 1937.
18. Hofmann, L.: Hämagiom der Trachea, Ztschr. f. Hals-, Nasen- u. Ohrenh. 44: 435-444, 1938.
19. Crafoord, C., and Lindgren, A. G.: Mucous and Salivary Gland Tumors in the Bronchi and Trachea, Acta chir. Scandinav. 92: 490, 1945.

THE HOSPITAL PROGRESS OF NINE HUNDRED NINETY-TWO PREMATURE INFANTS FED EVAPORATED MILK- CARBOHYDRATE MIXTURES

SEYMOUR GRUBER, M.D., ABRAHAM LITVAK, M.D., HENRY RASCOFF, M.D.,
AND ROBERT NORTON, M.D.
BROOKLYN, N. Y.

THE feeding of premature infants has assumed greater significance in recent years concomitant with the advances in our knowledge of the nutritional needs of these newborn infants. Along with this, there has been a reduction of the morbidity and the mortality and a shortening of the hospital stay. Many general principles have slowly evolved and have been more or less universally adopted for the care of the premature newborn infant, but the subject of the optimum type of feeding to be used is still controversial and a variety of milk preparations have been suggested. The belief that human milk is the only adequate food for these babies is no longer generally accepted. We are reporting a large series of premature babies, giving an analysis of the mortalities and a review of the results obtained using one type of artificial feeding, i.e., evaporated milk-Dextri-Maltose formulas.

In the four-year period between Jan. 1, 1944, and Dec. 31, 1947, there were 12,504 live births at the Beth-El Hospital. Of this group 992 of the infants were considered to be premature, approximately 7.9 per cent. This included all liveborn infants where there was any evidence of life, including heart beating or breathing. The standard for diagnosis of prematurity was any infant weighing less than 2,500 Gm. ($5\frac{1}{2}$ pounds) at birth regardless of the period of gestation, on the evidence that an infant of that size is not completely prepared for full, normal, independent, extrauterine life. This standard has been established by the American Academy of Pediatrics.

Analysis of the charts of these 992 infants has provided much interesting data, some of which is being presented in this initial paper. It must be emphasized at the outset that these results were obtained by an entire pediatric staff caring for a large number of babies.

A great deal has been written about the care and feeding of premature infants, but most of the papers have included relatively small series of babies. Many of the large maternity hospitals now have special provisions for the handling of their premature newborn infants. At the Beth-El Hospital a special premature nursery has been functioning since 1939. All babies weighing less than 5 pounds are sent directly and immediately from the delivery room to the premature nursery. The care of the baby in the nursery places special emphasis on individual nursing care, proper regulation of body temperature, suitable feeding, maintenance of body fluids, and prevention of infection. Although the

From the Department of Pediatrics, Beth El Hospital, Brooklyn, N. Y., Abraham Litvak, M.D., Director.

great majority of these babies are private cases under the individual care of the various members of the pediatric staff, a basic regime has been set up and there is seldom any marked variation from it. These infants are taken from the delivery room in preheated blankets directly to specially constructed incubators which automatically furnish an external environment of 85° F. to 95° F. and a relative humidity of 65 per cent. Oxygen is always supplied during the first twenty-four hours and as necessary thereafter. There is a minimum of handling, but any secretions present in the upper respiratory tract are aspirated with a soft rubber catheter. It is well known that premature babies require special skills in handling; hence our nursery is staffed only by nurses who are both interested in and competent to care for these tiny infants, and emphasis is placed on their judgment.

The basic regime followed is:

- A. Nothing by mouth for twelve to twenty-four hours.
- B. Sterile water offered in dram quantities during the second twelve-hour period.

C. During the second day the infant is offered small but increasing quantities of an evaporated milk-Dextri-Maltose formula in the proportion of one part of evaporated milk to two parts of water with 5 per cent Dextri-Maltose. The formula is given every two to three hours and, depending upon the capacity of the infant, the quantity is gradually increased. When there is not a suitable weight gain, in the judgment of the pediatrician, the formula is gradually concentrated in proportion to the maximum of one part of evaporated milk to one part of water with 5 per cent Dextri-Maltose.

Various methods of feeding are employed. If the infant is unable to suck or swallow, he is fed by gavage. If able to swallow, but not vigorous enough to suckle, the Breck feeder or a medicine dropper is used. When the infant has vigorous sucking and swallowing reflexes, he is allowed to nurse from the bottle.

All of these infants are given vitamin K by injection during the first twenty-four hours to obviate any possibility of hypoprothrombinemia. When one week old, a suitable multivitamin preparation is given to supply the metabolic needs of the infant for vitamins A, B complex, C, and D.

Emphasis is placed on aseptic technique; masks, caps, and gowns are always worn in the nursery and all possible means of preventing infections are employed. Penicillin and the sulfonamide drugs are readily used when indicated and where active infection is suspected the infant is removed to an isolation nursery.

The fluid requirements of the infants are met by the use of hypodermoclyses, intravenous clyses, and the intravenous administration of plasma or whole compatible blood. The procedures are again subject to the discretion of the individual pediatrician.

In this paper we are presenting an analysis of the mortality rate which prevailed during the above four-year period and a statistical summarization of the progress of the surviving infants.

MORTALITY RATE IN 992 PREMATURE LIVE BIRTHS AT BETH-EL HOSPITAL

The high mortality rate among premature infants can be ascribed to several causes, all associated with their underdevelopment which, when compared to normal infants, places them at a relative disadvantage. In general, they have poorly developed cardiovascular, nervous, respiratory, and digestive systems with high frequency of intracranial hemorrhage, weak reflexes, poor maintenance of body temperature, and poorly developed or atelectatic lungs with feeble respiratory movements, reduced gastric capacity, and impaired digestive and absorptive mechanisms.

Table I presents the over-all mortality picture for the four-year period and Table II the combined mortality by weight groups. Our over-all mortality rate of 13.5 per cent compares very favorably with the 26.8 per cent of Stoesser¹ and the 27.5 mortality rate reported by Hess.² It is interesting to note from Table III the time of death of the one hundred thirty-four infants. Well over one-half of the deaths took place within the first twenty-four hours and approximately three-fourths during the first two days of life. It must be stated parenthetically

TABLE I. PREMATURE LIVE BIRTHS AT BETH-EL HOSPITAL FROM JAN. 1, 1944, TO DEC. 31, 1947

	1944	1945	1946	1947	TOTAL
Lived	158	182	239	279	558
Died	26	37	40	31	134
Total	184	219	279	310	992
Mortality	14.1%	16.9%	14.2%	10.0%	13.5%

TABLE II. MORTALITY RATE BY WEIGHT GROUP

BIRTH WEIGHT (GM.)	1944	1945	1946	1947	TOTAL
To 1,000					
Births	13	12	16	9	50
Deaths	13	12	15	9	49
Mortality	100%	100%	93.8%	100%	98.0%
1,001 to 2,000					
Births	50	48	73	69	240
Deaths	10	17	20	16	63
Mortality	20%	35.4%	27.4%	23.2%	26.2%
2,001 to 2,500					
Births	121	159	190	232	702
Deaths	3	8	5	6	22
Mortality	2.5%	5.1%	2.6%	2.6%	3.1%

TABLE III. TIME OF DEATH OF 134 PREMATURE BABIES

YEAR	1 MINUTE	1 HR.	2 HR.	12 HR.	24 HR.	2 DAYS	4 DAYS
	TO 1 HR.	TO 2 HR.	TO 12 HR.	TO 24 HR.	TO 48 HR.	TO 4 DAYS	TO 21 DAYS
1944	5	1	5	4	8	2	1
1945	2	2	9	9	6	2	6
1946	2	5	8	5	9	5	6
1947	1	2	7	7	5	8	1
Total	10	10	30	24	28	18	14
Per cent of total deaths	7.5%	7.5%	22.3%	17.9%	20.9%	13.4%	10.5%

at this point that in some ways ours is a selected group of infants from the point of view that all of the mothers had either been private cases of our staff obstetricians or, if service cases, had been followed in our prenatal clinic. As a consequence, most of our mothers were in relatively good health with such factors as overwork and undernourishment playing only a small role in the premature deliveries. We had no cases of congenital syphilis. All of the infants in our series were born at the Beth-El Hospital; none were delivered elsewhere and subsequently brought to the nursery.

THE PROGRESS OF THE 857 SURVIVING PREMATURE INFANTS

The second part of this paper is a summarization of the progress of the 857 surviving infants. We wish to demonstrate how a large group of babies thrived under the care of a number of pediatricians, all of whom followed the basic regime given above. The importance of this work is to demonstrate a practical approach to prematurity which can be followed by anyone who undertakes the care of these infants. The evaporated milk-Dextri-Maltose formula is easily prepared, readily available, and requires no special skills, so that the mother can easily carry on with the care of her baby upon its discharge from the hospital.

Table IV presents a complete summary of the results obtained, divided into groups according to the birth weight in grams. This method of classifying the infants will make our results comparable to those of other authors. However, all of our weighings in the nursery are in terms of pounds and ounces; hence these figures are also shown. Gordon and his co-workers³ have found no distinction in the progress of male or females. As a consequence, we have grouped all of our cases together regardless of sex.

It will be noted from Table IV that the average day on which the birth weight was regained was 5.8 days, and that the average time for the smallest infants was 9.9 days, whereas the largest babies took only 5.1 days. When compared to the data of Hess² and Adams⁴ as demonstrated in Table V, our results are noteworthy. In each group our infants regained their birth weight the earliest.

From Table VI it will be found that in general the hospital stays of our babies were somewhat longer than those of the above authors. However, neither one states the weight at which the babies were discharged from the nursery. We have always made it a policy to keep our babies in the premature nursery until they weigh at least 5 pounds, 8 ounces. In general, our service cases have been retained in the hospital until they attain higher weights, especially during the winter months when we prefer to send them home at 6 pounds. However, many of our babies with birth weight over 5 pounds, but under 5 pounds 8 ounces, who are not as a rule cared for in our premature nursery unless they are very feeble, are sent home before achieving 5 pounds, 8 ounces as can be seen from Table IV, because we feel that they are not as delicate as the smaller infants, and admittedly, because of the limitations of nursery space and nursing personnel. We prefer to give the tiny infants the best we can offer.

The most important criterion of any feeding regime is, of course, the weight gain of the infants on it. All of our premature infants were fed the evaporated

PRAIRIE IV. ANALYSIS OF 857 SURVIVING INTRAMURAL PLANTS

TABLE V. AVERAGE DAY ON WHICH BIRTH WEIGHT WAS REGAINED

BIRTH WEIGHT (GM.)	DAYS		
	BETH-EL	ADAMS	HESS
1,000 to 1,500	9.9	13.9	18.6
1,501 to 2,000	8.3	12.8	14.4
2,001 to 2,500	5.1	10.8	11.8

TABLE VI. AVERAGE LENGTH OF STAY IN HOSPITAL

BIRTH WEIGHT (GM.)	DAYS		
	BETH-EL	ADAMS	HESS
1,000 to 1,500	50.7	45.3	45.7
1,501 to 2,000	32.2	30.7	30.5
2,001 to 2,500	11.5	17.7	19.9

milk-Dextri-Maltose formulas as shown above. We have used this type of feeding because we have felt that the babies do very well on it and because it lends itself readily to preparation in large amounts in our busy formula room. The formula is easily prepared, the sterility of the milk is assured, and there is uniformity of the product.

We have never found it necessary to resort to other types of feedings to achieve satisfactory weight gains; simple manipulations of the basic formula have been sufficient. From Table IV it can be noted how well our infants thrived on this formula. From the second to fourth weeks of life it is significant that our babies averaged a daily weight gain of 0.92 ounce. When broken down by weight groups as shown, the result is gratifying.

Gordon, Levine, and McNamara,³ in a recent report on the feeding of premature infants, have shown that "the use of mixtures of cow's milk . . . will produce larger gains in weight in premature infants than will human milk." A glance at Table VII will show that the mean weight gain per day in grams per kilogram of body weight that we obtained was comparable to that found by the above authors. We stress again that our series represents a practical approach to a large number of babies rather than an experimental program.

TABLE VII. COMPARISON OF MEAN WEIGHT GAIN FROM SEVENTH TO TWENTY-EIGHTH DAY

BIRTH WEIGHT (GM.)	MEAN WEIGHT GAIN IN GRAMS PER KILOGRAM PER DAY							
	BETH-EL		GORDON ET AL.					
	ALL EVAPORATED MILK		EVAPORATED MILK		HALF SKIMMED MILK		HUMAN MILK	
	GM.	CASES	GM.	CASES	GM.	CASES	GM.	CASES
1,000 to 1,500	15.3	28	14.9	14	17.3	31	11.7	4
1,501 to 2,000	12.7	149	13.7	23	14.2	36	12.7	12
2,001 to 2,500	10.9	680	--	--	--	--	--	--

SUMMARY

An analysis of 992 premature live births at the Beth-El Hospital is presented. These babies were all under the care of various members of the pediatric staff. All were fed and cared for according to a basic regime which is set forth in detail. The feedings were all evaporated milk-Dextri-Maltose formulas used in varying proportions.

Among the 992 premature babies there were 134 deaths, a mortality rate of 13.5 per cent. More than one-half of the deaths occurred during the first twenty-four hours and three-fourths during the first two days of life. In the group of infants weighing up to 1,000 Gm. at birth the mortality rate was 98 per cent. Where the birth weight was between 1,000 Gm. and 2,000 Gm. the mortality rate was 26.2 per cent and in the babies weighing between 2,000 Gm. and 2,500 Gm. there was a mortality rate of only 3.1 per cent.

The infants made noteworthy progress on the routine outlined. The average day on which birth weight was regained was 5.8 days with an average hospital stay of 16.4 days. Our babies made an average daily weight gain of 0.92 ounces (26.1 Gm.) during the second to fourth weeks of life and were discharged at an average weight of 88.7 ounces (2,514.6 Gm.). There was an over-all mean daily weight gain during the period from the second to fourth week of 11.2 Gm. per kilogram of body weight.

We feel that our babies have done exceptionally well on the evaporated milk-Dextri-Maltose regime outlined, and that its simplicity and uniformity, together with the excellent results herein reported, militate for its more general use in the care of premature infants.

We wish to commend the nursing staff of our nurseries without whom the excellent results reported in this paper could not have been attained.

The aid of Miss Leah Zahn and Miss Laura Shapiro, Record Librarians, was invaluable in the preparation of this report.

REFERENCES

1. Stoesser, A. V.: *The Management and Feeding of the Premature Infant. The Premature Infant and Multiple Births*; Carnation Co., Milwaukee, Wis., 1944.
2. Hess, J. H.: *The Premature Infant*, Brenneman's Practice of Pediatrics, Vol. I, chap. 43. Baltimore, 1946, W. F. Prior Co.
3. Gordon, H. H., Levine, S. Z., and McNamara, H.: *Feeding of Premature Infants*, Am. J. Dis. Child. 73: 442, 1947.
4. Adams, F. H.: *A Simple Formula for Premature and Full Term Infants*, J. PEDIAT. 33: 23, 1948.

MAJOR PELVIC PATHOLOGY IN CHILDREN

DANIEL W. GOLDMAN, M.D., F.A.C.S., AND PARKER K. HUGHES, M.D.
NEW ORLEANS, LA.

MAJOR pelvic pathology in children poses a significant problem to the gynecologist and the pediatrician. Although a large number of interesting case reports have been contributed to the medical literature, negligible attention has been paid to the actual incidence of these important entities. The advantages to be gained from such a study are self-evident, especially as these are related to diagnosis and treatment.

This paper has for its purpose the review of fourteen previously unreported cases which have been observed at Charity Hospital of Louisiana, New Orleans, and to evaluate these findings in terms of practical clinical application.

ANALYSIS OF CASES

In reviewing these cases we have been impressed with the fact that one-half of the patients presented a clinical picture of an acute abdomen. The findings in the remaining children suggested chronic intra-abdominal disease, thus making available more time for detailed diagnostic study.

I. CASES OF "ACUTE ABDOMEN"

In Table I are presented the salient features of the seven cases presenting acute abdominal emergencies. Five of the children were white and two were Negro, with ages ranging from 3 to 11 years.

An analysis of the symptoms presented reveals a rather constant finding of intermittent abdominal pain varying in duration from one and one-half to fourteen days prior to hospitalization. Vomiting was a prominent symptom in five cases, but its relation to the onset of acute pain was not clear, i.e., whether it preceded or followed the first attack of acute abdominal distress. The history of purgation following the onset of acute symptoms was present in four cases, with aggravation of symptoms in two cases.

Abdominal findings were consistent in all cases in respect to distention, tenderness, and rigidity. In two cases a mass was palpable. In only two of the seven cases was there a record of rectal examination. Leucocytosis was constant, varying from 10,500 to 22,200 white blood cells per cubic millimeter.

In no case was the correct preoperative diagnosis made. Acute appendicitis and its complications, undoubtedly a more common condition, was offered as the diagnosis in six cases, and diverticulitis with abscess in one case. The immediate and pathologic diagnoses revealed torsion of dermoid cysts in two instances.

From the Department of Obstetrics and Gynecology of Louisiana State University School of Medicine and Charity Hospital of Louisiana at New Orleans.
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TABLE I. Cases Presenting Clinical Picture of Acute Appendicitis

Vol. AND NAME	HISTORY	HABITS	PREGNANCY	DIAGNOSIS	OPERATIVE DIAGNOSIS	OPERATION
9 yr. Negro	Dull pain two weeks. Severe pain two days with vomiting.	Distention, rigidity, tenderness in right lower quadrant. Leuko- cytosis.	Aacute appendicitis. Possible appendi- cellitis.	Right dermoid cyst, 7 cm., with torsion of pedicle.	Salpingo- ophorectomy.	
10 yr. Negro	Dull pain right lower quadrant four days, generalized one and one half days. Pain increased in supine position, decreased in knee chest position. Purgation.	Generalized tenderness and rigid- ity. Mass in lower midabdo- men. Leucocytosis.	Ruptured appendix with encapsulated abscess,	Right dermoid cyst, 11 cm., with mas- sive hemorrhage and torsion of pedicle and of tube.	Salpingo- ophorectomy.	
10 yr. white	Pain and vomiting two days. Purgation.	Distention with generalized rigidity and tenderness. Len- cocytosis.	Acute appendicitis with possible rup- ture.	Left hemorrhagic cyst, 7 cm., of ovary with torsion of pedicle.	Salpingo- ophorectomy. Closure— accidental in- cision of blad- der. Abdomen drained.	
11 ^a yr. white	Pain and vomiting two days. Purgation.	Tenderness and rigidity in right lower quadrant. Mass palpable. Leucocytosis.	Acute suppurative appendicitis. Pos- sible abscess.	Right hemorrhagic cyst, 8 cm., with torsion of pedicle. Chronic appendi- ritis.	Salpingo- ophorectomy.	
3 yr. white	Recurrent pain three days with slight vomit- ing. Purgation.	Moderate tenderness, rigidity right lower quadrant. Disten- tion. Leucocytosis.	Acute appendicitis probable rupture.	Torsion of right tube with massive hemor- rhagic necrosis of tube and ovary.	Appendectomy.	
5 yr. white M.L.A.T.II	Acutely ill two days. Vomiting.	Generalized abdominal tender- ness and rigidity. Distention. Rec- tal examination—mass in pelvis. Leucocytosis.	Acute appendicitis with possible rup- ture and abscess formation.	Rupture of right pyo- salpinx with gener- alized peritonitis. Acute periappendi- ritis.	Appendectomy.	
11 yr. white	Acutely ill one and one- half days. Pain in left lower quadrant. Persistent vomiting.	Tenderness in left lower quadrant. No mass palpable. No disten- tion. Leucocytosis. Rectal examination negative.	Diverticulum of in- testine with abscess.	Hemorrhagic cyst, 7 cm., of left ovary with torsion of pedicle.	Oophorectomy.	

torsion of hemorrhagic cysts in three, torsion of tube and ovary in one, and ruptured pyosalpinx in one. It is interesting to note that in five of the seven cases the right adnexa were the seat of the pathology. This, perhaps, is responsible for the common preoperative diagnosis offered in six cases.

Treatment consisted of salpingo-oophorectomy in five cases, oophorectomy in one, and appendectomy and cecostomy in the remaining case.

The postoperative course was uneventful in five cases and prolonged in one case because of accidental bladder injury. The one fatality occurred six hours after operation and was due to overwhelming toxemia secondary to generalized peritonitis.

II. CASES OF "NONACUTE ABDOMEN"

Table II presents in summary form cases of the seven patients which entered the hospital with complaints of abdominal masses or symptoms of chronic abdominal pain. Of this group, five patients were white and two were negro with ages ranging from 18 months to 12 years. The three cases of ovarian malignancy occurred in a comparatively higher age group (10 to 12 years) and all these children were white.

The symptom of dull, aching, abdominal pain was the chief complaint in three cases, although an abdominal mass was also noticed prior to admission. The remaining four cases were brought into the hospital mainly because of slowly growing abdominal tumors. All three cases of ovarian malignancy gave histories of low-grade fever of several weeks' duration and in one of these there were associated nausea and vomiting.

Physical examination revealed palpable tumor masses in all cases, freely movable in six cases and apparently fixed in one instance. Rectal examination, although performed in six of the seven cases, was recorded as negative in all instances except one. Marked ascites was present in one case of malignancy necessitating aspiration before a definite mass could be palpated; pleural effusion was an interesting associated finding in this case. Additional diagnostic x-ray studies, barium enema, and pneumoperitoneum were of no apparent value except in confirming the presence of an abdominal tumor mass.

The correct diagnosis was made or suspected in six of the seven cases. Ample time for investigation and the absence of abdominal muscle spasm were contributory to the greater diagnostic accuracy in this group.

The pathologic diagnoses revealed dermoid cysts varying from 4 to 10 cm. in diameter to be present in four cases, and malignancies in the remaining three, two being sarcomas and one a papillary adenocarcinoma.

Treatment consisted of oophorectomy in three cases and salpingo-oophorectomy in one case for the benign cysts, and oophorectomy in one instance and salpingo-oophorectomy in the two cases in the malignant group. Postoperative radiation was used in the cases with malignant tumors.

The postoperative course was uneventful in all cases.

TABLE II. CASES PRESENTING ABDOMINAL MASSES OR HISTORY OF CHRONIC ABDOMINAL PAIN

AGE AND RACE	MATERIAL	FINDINGS	PREOPERATIVE DIAGNOSIS	POSTOPERATIVE DIAGNOSIS	OPERATION
2 yr. Negro	Abdominal tumor.	Mass in lower left quadrant, freely movable, not tender. Rectal examination and barium enema negative.	Possible ovarian tumor.	Dermoid cyst, 5 cm., of left ovary.	Oophorectomy.
10 yr. Negro	Dull pain in abdomen two months and mass one month increasing in size. Pain relieved in supine position.	Mass freely movable, palpable 2 fingers above umbilicus. Rectal barium enema, x-ray, negative.	Ovarian cyst vs. omental cyst.	Right dermoid cyst, 10 cm.	Oophorectomy, Appendectomy.
9 yr. Negro 18 months white	Mass and dull pain in abdomen two months. Mass in lower abdomen one week.	Cystic mass palpable rectally and abdominally, freely movable. Palpable mass in umbilical area, freely movable. Aspiration of cyst—20 cc. X-ray after pneumoperitoneum. Rectal examination, negative.	Ovarian cyst.	Right dermoid cyst, 7 cm.	Sulpingo-oophorectomy.
12 yr. white	Painless swelling of abdomen two weeks. Slight fever.	Ascites, paracentesis—3,500 c.c. bloody fluid. Mass palpable filling entire lower abdomen, freely movable. Associated pleural effusion. X-ray of abdomen and barium enema, negative. Rectal examination, negative.	Retropertitoneal tumor.	Right dermoid cyst, 9 cm.	Oophorectomy.
10 yr. white	Several attacks of dull pain in abdomen during month.	Abdomen distended. Indefinite mass palpable. No rectal examination. Low-grade fever.	Retropitoneal tumor vs. ovarian tumor.	Papillo-adenocarcinoma of right ovary, 18 x 10 x 5 cm.	Right salpingo-oophorectomy.
10 yr. white	Mass noted in abdomen three weeks. Slight fever. Occasional bouts of vomiting. No pain.	Tender, movable mass in right lower quadrant. Rectal examination, negative.	Possible ovarian tumor.	Round-cell sarcoma of right ovary, 12 x 14 cm. Myxostroma, right ovary.	Right oophorectomy, Resection of omentum. Right salpingo-oophorectomy.

PATHOLOGY

Table III presents the pathologic distribution in this series.

Although the series is small, the occurrence percentages are comparable with the cases reported by Loeb and Levy.¹

TABLE III. PATHOLOGIC DISTRIBUTION

TYPE OF PATHOLOGY	NO.	%
A. Benign		
Dermoid cyst of ovary	6	42.95
Hemorrhagic cyst of ovary	3	21.5
Torsion of tube	1	7.1
Ruptured pyosalpinx	1	7.1
B. Malignant		
Sarcoma		
Round cell	1	7.1
Myxosarcoma	1	7.1
Carcinoma		
Papillary, adenocarcinoma	1	7.1
	14	100

INTERPRETATION

The necessity for routine rectal examination, preferably while the child is under the influence of sedation, cannot be overemphasized. It is important, however, to bear in mind that ovarian tumors may be pedunculated, and these are frequently abdominal rather than pelvic.

Although surgical management (i.e., exploratory laparotomy) of these cases is unchanged regardless of the findings on rectal examination, the attainment of an accurate preoperative diagnosis is of more than academic importance to the surgeon.

While physiologic cysts in the adult rarely require treatment or cause complications, the reverse is noted in the child where the weight is frequently the cause of torsion, not only of the pedicle but also of the adjacent tube.

Although three cases are reported as hemorrhagic cysts, it is felt that this phenomenon was secondary to torsion, which occurred in all cases, and belies the true nature of the pathology.

As estrogen can be demonstrated in the blood stream and urine of children between 8 and 10 years of age, one may assume that pituitary stimulation is present and follicle cyst formation may, therefore, be rationally explained.

DISCUSSION

The chief purpose of this study is to present a logical diagnostic routine to be employed when pelvic pathology is suspected in the prepuberal period.

The importance of a carefully obtained, detailed history is self-evident. A significant error, however, can be committed by underestimating or ignoring the history of a child and relying completely on the mother's interpretation of symptoms.

Below are listed the characteristics of the more frequently encountered symptoms applicable to pelvic pathology:

1. *Pain.*—(a) *Acute:* Acute pain, if sudden in onset, frequently indicates torsion of an ovarian cyst or rupture of a cyst with associated immediate peritoneal reaction. Both may be accompanied by symptoms of shock. Attention should be paid to circumstances preceding pain, such as falling, direct trauma to abdomen, weight-lifting, urination and defecation, all of which may be the cause of sudden torsion. At the onset pain is usually localized to the affected side but soon becomes generalized due to peritoneal reaction.

(b) *Chronic:* Chronic pain may assume the form of recurrent attacks of variable duration. Pain is usually localized to the affected side. Partial torsion of a cyst is suggested by a history of relief of pain when the patient assumes a certain posture. Chronic pain may also result from pressure on the peritoneum from ovarian tumors or from low-grade inflammatory processes.

2. *Nausea and Vomiting.*—Nausea and vomiting may be due to pain, if severe, or to sudden peritoneal irritation in cyst torsion or rupture. It may precede or occur concurrently with these conditions. The frequent occurrence of reflex vomiting in children should always be kept in mind.

3. *Fever.*—Low-grade fever is frequently associated with malignancies but usually absent in benign cysts unless these are complicated by torsion or rupture. The tendency of many children to suffer marked febrile reactions which are not commensurate with the severity of the disease makes the temperature chart difficult to evaluate. Furthermore, acute inflammatory processes frequently present little or no fever at the onset of the disease. The degree of fever cannot be regarded as pathognomonic in the differential diagnosis of pelvic pathology.

4. *Abdominal Mass.*—A notation should be made as to location when first observed, as this may indicate its point of origin. The rate of growth is also a valuable diagnostic aid.

5. *Vaginal Bleeding.*—Vaginal bleeding of any amount is important. It may indicate precocious puberty or symptoms of feminizing ovarian tumors.

EXAMINATION

General.—Inspection of the patient for the occurrence of secondary sex characteristics may make available significant information as regards granulosa cell tumors as well as pituitary and adrenal disorders.

Abdominal.—Details of technique will be omitted except to mention the general principles to be observed: (1) gain confidence of child, (2) mild sedation, especially in the nervous child, (3) extreme gentleness at all times.

The prone position for abdominal palpation may be employed, thus allowing the rebound mechanism to be better demonstrated. Attention is called to the finding that tumors of pelvic origin are most frequently abdominal in location and palpation of even mid and upper abdominal masses does not exclude or minimize the possibility of pedunculated ovarian neoplasms.

Pelvic.—Sehaufler's² description of gross anatomical development from birth to 10 years of age offers a suitable standard of normal findings. Knowledge of these facts is prerequisite to the accurate interpretation of data secured from a properly performed pelvic examination. The cardinal points are quoted from the original text:

1. A cervix much longer in proportion to the corpus (a ratio of approximately 3:1)
2. An almost total lack of anteflexion which characterizes the adult uterus
3. A position more nearly in the axis of the birth canal
4. A relatively meager vascular and lymph supply—satisfactory only for purposes of normal nourishment.

In the immediate preadolescent period (ages 10 to 12) growth is accelerated and gross characteristics soon resemble those of the adult.

For the inexperienced examiner of children a rectal bimanual examination is preferable to a vaginal examination, even if the latter is possible. The interposition of the rectal wall facilitates in delineating the uterus and cervix as well as associated pathology. Whenever possible, vaginal examination may reveal additional important information and should not be neglected if rectal examination is indefinite.

A necessary prerequisite to either method of examination is an empty bladder.

Rectal examination will reveal the presence of a mass in many cases. By gentle use of the little finger, well lubricated, much information may be obtained. If no mass is palpable the pelvic origin of an abdominal tumor may frequently be confirmed and localized by employing the reverse bimanual examination as proposed by Rankin and Eger.³ This consists of applying intermittent sharp pressure on the tumor in a superior direction which produces tension on the pedicle and broad ligament, readily palpable by the rectal finger. In the case of small movable tumors, repeated rectal examination is advisable and frequently necessary before palpation is possible. Fortunately the tendency of small ovarian masses to prolapse into the cul-de-sac makes eventual palpation possible.

When inflammatory conditions are suspected, induration or fluctuant masses in the cul-de-sac are usually easily palpated. Gentleness is again necessary to prevent dissemination of localized or encapsulated infection.

ADDITIONAL DIAGNOSTIC AIDS

When the clinical picture does not suggest a surgical emergency, the following additional diagnostic aids may be employed in order to arrive at the correct diagnosis:

1. *X-ray*.—The chief value of x-ray is the revelation of calcification within the mass, almost definitely labeling the tumor as a teratoma but not differentiating between the benign cyst and the malignant solid type. X-rays of the long bones to demonstrate precocious growth are also used as an adjunct to the diagnosis of feminizing tumors.

2. *Cystoscopy and Pyelograms*.—In order to rule out definitely congenital anomalies of the urinary tract and kidney tumors, these procedures may frequently be necessary.

3. *Aspiration of Cyst*.—Unfortunately this procedure is occasionally employed, despite the apparent dangers and questionable diagnostic value. It is

usually performed only in large, well-demarcated cysts lying flush to the abdominal wall in which surgery is indicated regardless of pathology. The characteristic fluid from cystic teratomas will certainly identify the tumor, but the obvious dangers in aspiration of malignant cysts preclude this procedure as a safe one.

4. *Pneumoperitoneum*.—Although advocated by some, the value of this procedure is questionable and the technical difficulty and added expense do not justify its wide use in these cases.

CONCLUSIONS

1. Major pelvic pathology is an important and not infrequent cause of symptoms referable to the abdomen in children.
2. Knowledge of the normal anatomy of the prepuberal female child is essential for the proper evaluation of pelvic findings.
3. A thorough acquaintance with pelvic pathology in the prepuberal female is essential in making the diagnosis clinically as well as at the operating table and in performing the indicated conservative or surgical treatment.
4. The child with abdominal pain is frequently first seen by the pediatrician and general surgeon. The greater relative incidence of acute appendicitis usually determines the course of treatment. More frequent consultation with the gynecologist is recommended in cases involving female children. This is especially applicable to atypical cases of acute abdomen as well as cases presenting abdominal symptoms of relatively long duration.
5. An outline for routine examination of the prepuberal female is presented.

REFERENCES

1. Loeb, M. J., and Levy, W.: Cysts and Tumors in Children Under Ten Years of Age, With Report of Case of Teratoid Cyst in Child Four Years Old Simulating Acute Appendicitis, *Arch. Pediat.* 49: 651-666, 1932.
2. Schaufler, Goodrich Capen: *Pediatric Gynecology*, Chicago, 1942, Yearbook Publishers, Inc.
3. Rankin, L. M., and Eger, S. A.: Pedunculated Ovarian Cysts in Children, *Am. J. Surg.* 60: 140-141, 1943.

Case Reports

TYPHOID FEVER TREATED WITH CHLOROMYCETIN

RALPH STILLER, M.D.
ALEXANDRIA, VA.

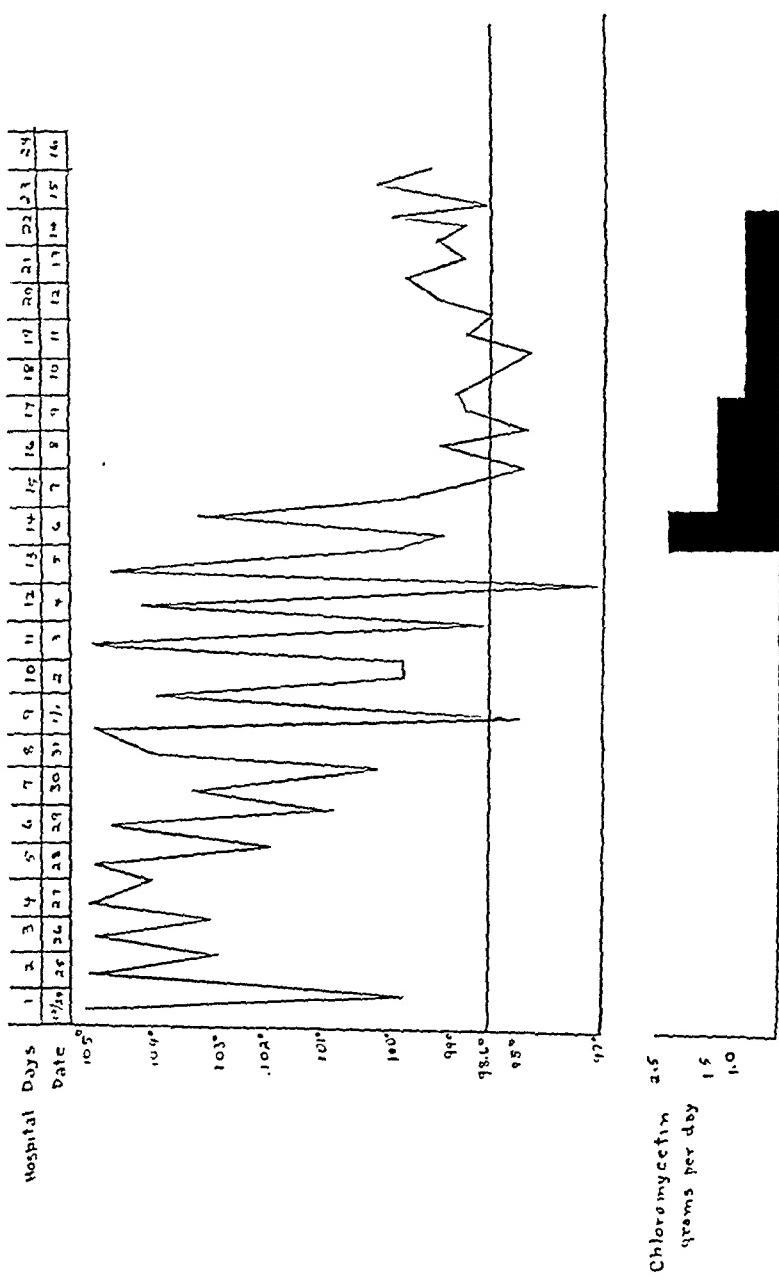
CHLOROMYCETIN has recently been reported efficacious in the treatment of typhoid fever by Woodward, Smadel, and collaborators,¹ and this case is presented as a contribution to the clinical literature on the subject. The drug has shown no toxic effects in previous usage with scrub typhus and endemic typhus. It is rapidly absorbed from the intestinal tract and either rapidly excreted or inactivated. These investigators treated ten typhoid patients by the tenth day of the illness, noted marked improvement in the clinical picture within twenty-four hours, and achieved a permanent normal temperature within three and a half days, on the average, from the start of the treatment. None of their patients died; two relapsed and were promptly cured by readministering the drug. It is of interest that the organisms isolated from the relapsed cases showed no increased resistance to the drug. Of their control patients, one died and the remaining seven ran an average course of thirty-five days. All of their patients were adults. Their dosage schedule was 50 mg. per kilogram body weight as an initial dose followed by 0.25 Gm. every two hours until the temperature was normal, then every three to four hours for five days.

CASE REPORT

S. C., a 6½-year-old white female, was admitted to Children's Hospital, Washington, on Dec. 24, 1948, with a chief complaint of temperature to 105° F. of five days' duration and a mild hacking cough. At the onset the temperature would rise to 102° F. but over the five-day period despite sulfadiazine and later intramuscular penicillin, when the former drug was vomited, the temperature continued to climb. A slight cough developed with the onset of the illness but was not a prominent symptom. There was no history of ingestion of raw milk or contaminated water. About four weeks previously the family had motored to another city and had eaten along the way.

On admission physical examination revealed an acutely ill child, coughing occasionally, hot and flushed, and moderately dehydrated. The pharynx was slightly injected, and ears, chest, and abdomen were entirely negative. Blood pressure was 120/78. Chest x-ray was negative as was the blood culture and heterophile antibody reaction. The urine showed some acetone but was otherwise negative. The initial blood count showed 4.4 million erythrocytes, hemoglobin 12.5 Gm., leucocytes 11,600 with 68 per cent neutrophiles of which 55 were segmented, 12 stab forms and one juvenile. Lymphocytes were 27 per cent, eosinophiles 1 per cent, basophiles 1 per cent, and monoeytes 3 per cent. Purified protein derivative No. 1 was negative at forty-eight and seventy-two hours. Subsequent white blood counts showed no substantial change.

Penicillin 300,000 units a day was given intramuscularly for the first three hospital days until it became apparent that it was of no benefit and was discontinued. During this first hospital week the temperature became plateau-like, never dropping below 103° F. and ranging to 105° F. Therapy was entirely supportive, consisting of intravenous administration of vitamins B and C, and



	35	24	23	22	21	20	19	18	17	16	15	14	13	12	11	10	9	8	7	6	5	4	3	2	1
24 hour urine + faec.																									
Blood Cultures	-	+																							
Stool Cultures	-	-																							
"O" Antigen																									

Chloramycetin blood level (ug/ml)
24 hour urine + faec.
Blood Cultures
Stool Cultures
"O" Antigen

amino acids. A high protein, soft diet was instituted and fluids were forced. On the fifth hospital day several small pink macules that blanched on pressure were noted on the abdomen and extremities. At that time the liver extended a few fingerbreadths below the costal margin, and the abdomen was slightly distended and felt somewhat doughy on palpation. The liver continued to enlarge until at height of the illness it extended down to the level of the umbilicus. The spleen could be felt as a soft tumor on the seventh hospital day. Diagnosis of typhoid fever was confirmed that same day with a reported agglutination of O antigen in a dilution of 1:320 and H antigen in a dilution of 1:640. Similar studies done two days previously had been reported as negative. Confirmatory blood culture was reported two days later. Further laboratory data of significance are reported on Chart I. The clinical course was typical with the temperature spiking daily to 105° F. for the second hospital week. There was a steadily worsening anemia which was combated by two transfusions of 250 c.c. each of whole blood.

On Jan. 6, 1949, the nineteenth day of the illness, chloromycetin was started with an initial dose of 1 Gm. calculated on the basis of 50 mg. per kilogram of the body weight followed by 0.25 Gm. every four hours. The temperature dropped to 100° F. within sixteen hours and from then on stayed below 100° F. After forty-eight hours of normal temperature the dose was decreased to 0.25 Gm. every six hours and continued for five more days. There was one positive stool culture for *Eberthella typhosa* noted on the day following initiation of treatment and none after that. During the week of normal temperature the patient's general condition improved markedly and the liver and spleen steadily receded in size. She was discharged home on her twenty-fourth hospital day after nine days of normal temperature, twenty-eight days after the onset of the disease. Follow-up at home showed an uneventful convalescence. Subsequent stool cultures have remained negative.

COMMENT

The pertinent observation may be made concerning this case that since the drug was not started until the nineteenth day of the illness the defervescence is not conclusive. However, the rather sudden response within twelve hours, when the febrile curve had given no evidence of beginning lysis, the fact that in typhoid fever the resolution is usually by lysis over a three- to five-day period, coupled with the rather dramatic results reported by Woodward, leads me to feel that the course of this illness was shortened at least by a few days and that the subsequent negative stools, a positive one having been reported the day that therapy was begun, can be credited to the action of this antibiotic.

Facilities were available for determining chloromycetin levels in the blood and urine. The blood specimens were drawn three hours and five hours, respectively, after the drug was given, depending on whether the patient was on a four- or six-hour dosage schedule. They therefore represent the low point of blood concentration on these two dosage routines. Insofar as *E. typhosa* is inhibited in vitro by a concentration of 0.25 gamma per cubic centimeter, it can be seen that these reported levels are well above the theoretical minimum and it probably will be unnecessary in the future to follow cases with routine blood concentration determinations.

The author wishes to thank Miss Sarah Stevens for her technical assistance in determining the chloromycetin levels.

REFERENCE

1. Woodward, Smadel, et al.: Ann. Int. Med. 29: 131, 1948.

NEPHROCALCINOSIS AND PSEUDOMONAS AERUGINOSA
PYELONEPHRITIS: TREATMENT WITH p-AMINOMETHYLBENZENE-
SULFONAMIDE (SULFAMYLYON)

ROBERT C. RUTLEDGE, JR., M.D., W. G. KLINGBERG, M.D., AND
M. LAWRENCE HEIDEMAN, JR., M.D.
ST. LOUIS, Mo.

THE purpose of this report is to describe a case of nephrocalcinosis with pyelonephritis due to infection with *Pseudomonas aeruginosa* and the results of treatment with Sulfamylon.*

The properties of Sulfamylon which are of interest have been described previously.¹⁻⁸ It is much more soluble than other sulfonamides, is not opposed in its action by p-aminobenzoic acid, and, although its range of antibacterial action is similar to that of other sulfonamides, other organisms such as the Clostridia are susceptible to its action. As will be seen later, some strains of *Ps. aeruginosa* are particularly sensitive to sulfamylon.

R. B., a 14-year-old white girl, was referred to Dr. Alexis F. Hartmann in October, 1946, because of the persistence of a urinary tract infection which had not yielded to treatment with penicillin, sulfonamide drugs, or mandelic acid. Studies of the urinary tract had revealed the presence of numerous areas of calcification throughout the kidney substance. The present illness is believed to have begun at the age of 7 years with a rather severe febrile illness accompanied by nausea, vomiting, and cramping abdominal pain. Thereafter similar but less severe attacks lasting two to three days had recurred at yearly intervals but had recently increased in both frequency and duration. During these times the urine was cloudy, and on occasion gross blood had been observed. Although sulfonamide drugs and mandelic acid had been of temporary benefit on several occasions, each soon became ineffectual. During the preceding year the patient had lost appetite and weight due to her frequent illnesses.

The patient was admitted to the Children's Hospital for study on Oct. 25, 1946, shortly after an unusually severe attack of her illness. Physical examination revealed a thin, pale, white girl who appeared to be chronically ill. There was bilateral tenderness to palpation in both flanks, but the remainder of the examination, including funduscopic, was negative. Blood pressure was 128 systolic over 80 diastolic. Chemical examination of the blood revealed serum calcium 12.7 mg., phosphorus 3.7 mg., nonprotein nitrogen 38 mg. per 100 ml., respectively. An Addis-Shevky test revealed a volume of 845 ml. of acid urine with a specific gravity of 1.009, red blood cells 66,000,000, white blood cells 150,000,000. There was a trace of albumin. Maximum urea clearance was 140 per cent of normal. A catheterized specimen of urine was cultured and revealed *Escherichia coli* sensitive to 0.1 unit per milliliter of streptomycin. Intravenous pyelogram revealed no abnormalities of the pelvis or calices, but scout films revealed numerous areas of calcification throughout both kidneys (Fig. 1). In an effort to rule out hyperparathyroidism, other areas of calcification in the lungs, stomach, and choroid plexus were searched for but not found. Areas of decalcification of other bones of the body were not seen. Two twenty-four hour

*From the Department of Pediatrics, Washington University School of Medicine, and the St. Louis Children's Hospital.

*Sulfamylon is the trade name of the product made by Winthrop-Stearns Inc., who kindly supplied the material used in this study. For convenience, the name Sulfamylon will be used throughout this paper in place of p-aminomethylbenzenesulfonamide.

specimens of urine were collected and analyzed, one containing 206, the other 233 mg. of calcium. This was considered to be within normal limits. The basal metabolic rate ranged from minus 3 to plus 8 per cent on the basis of the Wetzel Grid.

Treatment with streptomycin was begun, and after five days the urine was again cultured, revealing *E. coli* sensitive to 2 units per milliliter of streptomycin. The patient was discharged from the hospital on Nov. 8, 1946, taking Sulfamerazine 0.05 Gm. per kilogram per day. At home the patient continued to have afternoon fever, headache, backache, and poor appetite.



Fig. 1.—Film of abdomen showing renal calcification

On Dec. 2, 1946, Sulfamerazine was discontinued because of the development of leucopenia, and mandelic acid was substituted. However, on Dec. 4, 1946, because of increasing fever and flank pain, she was again admitted to the hospital where she was found to have a temperature of 41° C. and mild acidosis. Chemical examination of the blood revealed a serum carbon-dioxide content of 47.0 volumes per cent, calcium 11.5 mg., phosphorus 3.0 mg., and nonprotein nitrogen 47.0 mg. per 100 ml., respectively. Urine culture revealed *E. coli* and *Alkaligenes faecalis*. Treatment with streptomycin was begun, and over the next five days the temperature gradually fell to normal and the urine was found to

be sterile. She was discharged from the hospital on Dec. 14, 1946, taking mandelic acid. During the next seven days her temperature gradually increased; her urine was noted to be cloudy and had a slightly greenish color. Culture revealed *Ps. aeruginosa*. On Dec. 19, 1946, there was a chill followed by a temperature of 40° C., and she was again admitted to the hospital. At this time she was acutely ill, dehydrated, and listless, with a temperature of 40° C. Blood pressure was 135/100. Chemical examination of the blood revealed serum carbon-dioxide content of 53 volumes per cent, nonprotein nitrogen 66 mg., calcium 10.2 mg., phosphorus 3.6 mg. per 100 ml. The urine was loaded with pus cells and had a greenish tint. Dehydration was corrected with parenteral fluids, and streptomycin was again administered. Over the next four days her fever persisted, and the nonprotein nitrogen gradually rose. At this time the results of the initial urine culture revealed *Ps. aeruginosa* sensitive to 10 mg. per cent of Sulfamylon. Because of the possibility that the *Ps. aeruginosa* was masking other organisms, streptomycin was continued, and Sulfamylon in doses of 2 Gm. every four hours by mouth was begun. During the following three days her temperature returned to normal but she became more lethargic and developed deep, rapid, pauseless, respiration. At that time her serum carbon-dioxide content was 17.5 volumes per cent with a pH of 7.0, sodium chloride 664 mg., and nonprotein nitrogen 83 mg. per 100 ml. In addition, phosphorus had risen to 6.4 mg. per 100 ml. Her temperature spiked to 40° C. At 9:40 A.M. on Dec. 30, 1946, she was given 30 ml. per kilogram of $\frac{1}{6}$ molar sodium-r-lactate intravenously and a mixture containing 30 ml. per kilogram of $\frac{1}{6}$ molar sodium-r-lactate and 40 ml. per kilogram of hypotonic Ringer's solution subcutaneously. This mixture is known as "half fortified" lactate Ringer's. Six hours later at 3:40 P.M. her serum carbon-dioxide content was 49 volumes per cent with a pH of 7.4, and she was again alert and cooperative. The next morning the serum nonprotein nitrogen was 53 mg. per 100 ml., but the carbon-dioxide content had fallen to 37 volumes per cent. Oral molar sodium lactate in doses of 100 c.c. per day was started in an effort to prevent the development of acidosis. On Jan. 9, 1947, Sulfamylon was discontinued, and culture of the urine again revealed *Ps. aeruginosa* still sensitive to 10 mg. per 100 ml. Sulfamylon. The drug was continued, and on Jan. 23, 1947, after being afebrile for five days, she was discharged from the hospital taking Sulfamylon one gram every four hours and molar lactate 100 c.c. per day.

At home she experienced some nausea after taking Sulfamylon but remained fairly well until on Feb. 7, 1947, the Sulfamylon was discontinued because of increasing nausea.

Five days later she had a chill with fever to 39° C. and the next morning had nausea, flank pain, and fever. On Feb. 14, 1947, she was admitted to the hospital for the fourth time with a temperature of 40° C., appearing acutely ill but not dehydrated. Chemical examination of the blood revealed nonprotein nitrogen 42 mg., calcium 12.9 mg., phosphorus 4.1 mg. per 100 ml. Urine culture revealed *Ps. aeruginosa* sensitive to 10 mg. per cent Sulfamylon. Treatment with Sulfamylon, 1.5 Gm. every four hours, was begun, and five days later her temperature was normal. Her maximum urea clearance at this time was 30 per cent. She was discharged on March 1, 1947, receiving 6 Gm. of Sulfamylon a day. At home she continued to be fairly well, occasional spikes in temperature being controlled with increased doses of Sulfamylon up to 12 Gm. per day. During the next three months the patient gained weight, felt better, and became more active, but continued to have fever occasionally and complained of nausea after taking Sulfamylon. Although there were occasional spikes of temperature accompanied by some flank pain, the dose of Sulfamylon was gradually decreased as she improved until on June 14, 1947, she was taking

4 Gm. per day. During this period of time there was no evidence of leucopenia or anemia. However, on June 17, 1947, she developed chills and temperature to 38.6° C. accompanied by flank pain. Sulfamylon was increased to 12 Gm. daily, but by June 19, when no improvement had occurred, she was admitted to the hospital where *E. coli* was cultured from the urine. This organism was subsequently found to be sensitive to 10 mg. per 100 ml. of sulfadiazine, Sulfamerazine, Sulfapyrazine, sulfathiazole, and sulfanilamide and to 0.5 unit per ml. of streptomycin. In the meantime Sulfamylon was administered in doses of 10 Gm. per day. Bilateral retrograde pyelograms were obtained, following which the catheters were left in place to provide for continuous irrigation of streptomycin solution. A repeat urine culture later showed both *E. coli* and *Ps. aeruginosa*. The patient was discharged on June 26, receiving Sulfamerazine 0.05 Gm. per kilogram per day and Sulfamylon 6 Gm. per day. The last urine culture had shown only *Ps. aeruginosa*. Calcium excretion studies were repeated, and on three successive days twenty-four-hour urine specimens were analyzed, showing a daily calcium excretion of between 320 and 335 mg. per day, when she was on a calcium intake of 1 Gm. (20 Gm. per kilogram) which was at the upper limits of normal according to Knapp.⁹

At home she continued to take Sulfamylon, but because of intolerance to Sulfamerazine she was given sulfathiazole. She was afebrile until August 9, when Sulfamylon was stopped, following which there was a spike in temperature which was not readily controlled with either Sulfamylon or sulfathiazole. However, in contrast to her previous episode, she felt well, and hospitalization was delayed until August 25, when she was admitted with fever, flank pain, slight dehydration, and rapid, deep respirations. Chemical examination of the blood revealed a nonprotein nitrogen of 76 mg., carbon-dioxide 27.7 volumes, Calcium 10.1 mg., phosphorus 3.7 mg. per 100 ml. Sulfamylon was given in doses of 12 Gm. per day. Parenteral fluids were given as before to correct the acidosis. After three days the temperature had become normal, and on Sept. 1, 1947, a urine culture showed *Ps. aeruginosa*. She was discharged taking 10 Gm. Sulfamylon per day.

At home until Nov. 24, 1947, she continued to take Sulfamylon in doses ranging from 6 to 12 Gm. per day. On repeated visits to the clinic her non-protein nitrogen was between 45 and 50 mg. per 100 ml. She gained weight, felt much better, and again resumed much activity. Rare spikes in temperature were controlled with increased doses of Sulfamylon. On Nov. 24, 1947, culture of a catheterized urine specimen was reported to be sterile. However, for the most part repeated urine cultures always showed a few colonies of *Ps. aeruginosa*. It is of interest that during this first year that she had received Sulfamylon the sensitivity of the organism increased only from 10 mg. per cent to 30 mg. per cent.

On March 27, 1948, she felt well enough to go back to school but became very depressed over her illness and was allowed to drop out. She continued occasionally to have low-grade fever and on May 8, 1948, for the first time experienced renal colic and passed a few small stones. Following this she continued to be fairly well but on Aug. 28, 1948, again had colic and passed more stones, analysis of which showed them to be composed of calcium phosphate and oxalate in about equal amounts.

On Oct. 1, 1948, she started school.

Since the last period of hospitalization there has been little change in the laboratory findings. The urine has consistently been of low specific gravity, containing a trace to one plus protein and numerous pus cells. Cultures reveal *Ps. aeruginosa*. The serum nonprotein nitrogen varies between 40 and 60 mg. per 100 ml. and the calcium and phosphorus have been within normal limits.

Clinically, she has shown rather steady improvement as regards her sense of well-being, especially since being allowed to resume more normal activity. One comforting observation is that her blood pressure has remained within normal limits during this period.

At this writing she has been taking Sulfamylon for almost two years in doses ranging from 6 to 12 Gm. per day along with molar sodium lactate in doses depending on repeated determinations of serum carbon-dioxide content. There have been no toxic reactions other than occasional nausea. On Sept. 1, 1948, the *Ps. aeruginosa* was sensitive to 20 mg. per 100 ml., and on Nov. 11, 1948, showed no growth even in 10 mg. per 100 ml. of Sulfamylon.

DISCUSSION

Obviously this patient has not been cured by Sulfamylon. Undoubtedly there are obstructive phenomena, small abscesses, and much tissue necrosis surrounding the areas of calcification, providing a fertile field for bacterial growth and little chance for free drainage. That the prognosis is ultimately poor is evident. However, we feel that the use of Sulfamylon has prevented rapid progression of the disease and has prolonged the life of the patient.

The character of the renal disease is vague. The urine is of low specific gravity; albuminuria is not prominent, and there is no hypertension in the absence of acute infectious episodes. Nitrogen and phosphate retention are not present to an excessive degree. Therefore, one would be inclined to believe that the lesion is predominantly tubular in location.

Several interesting features of this case bear attention:

1. The failure of any one agent other than Sulfamylon to control the *Ps. aeruginosa* infection as is well-demonstrated by the repeated acute episodes following withdrawal of the drug.

2. The absence of anemia, leucopenia, skin rash or other toxic manifestation and the failure of the organism to develop appreciable resistance to the therapeutic agent even after a period of two years of treatment. That Sulfamylon does produce some nausea when taken by mouth became evident early in her course, and, although every effort was made to substitute another more palatable drug, it was realized both by us and by the patient that only Sulfamylon offered the relief which she sought.

3. The episode of severe acidosis on Dec. 29, 1946, occurred during a period in which the urea clearance was supernormal. This is usually interpreted as reflecting tubular damage. Since that time a patient with hydronephrosis and presumably tubular damage has been treated with Sulfamylon and became markedly acidotic within two days. After correction of the acidosis he was placed on oral molar sodium lactate and has since remained free of acidosis. These observations led to an investigation of the effects of Sulfamylon on the formation of urine.¹⁰ The ingestion of this drug is followed within a few hours by the excretion of markedly alkaline urine, the pH of which often approaches that of blood. This base loss persists for only a short time in normal individuals and is prevented by the previous administration of ammonium chloride. These findings are similar to those of Hartmann and associates¹¹ in their study of the effects of sulfanilamide on acid-base balance. Apparently the normal individual is able to recover from the effects of Sulfamylon on the renal tubules in a few hours. However, the fact that two patients with tubular damage were precipitated into acidosis by the administration of Sulfamylon would seem to indicate that in the face of diminished tubular reserve one should give extra alkali.

SUMMARY

A case of nephrocalcinosis complicated by persistent *Ps. aeruginosa* infection is presented and the results of treatment with Sulfamylon discussed. That

Sulfamylon has been effective seems to be evident by the repeated episodes of severe illness following withdrawal of this drug. During a period of two years in which Sulfamylon has been given in doses ranging from 6 to 12 Gm. per day, no appreciable toxic reactions have been observed, and the infecting organism has shown little tendency to develop resistance to this agent. Sulfamylon may cause severe acidosis due to base loss in the urine, especially in the presence of renal tubular damage, and should be administered along with sufficient alkali to prevent this complication. For this purpose we have routinely employed a one molar solution of sodium lactate in doses ranging from 3 to 5 ml. per kilogram body weight per day, depending on the serum carbon-dioxide content.

REFERENCES

1. Goetchius, G. R., and Lawrence, C. A.: J. Baet. 49: 575, 1945.
2. Welch, A. D.: Physiol. Rev. 25: 687, 1945.
3. Lawrence, C. A.: J. Baet. 49: 149, 1945.
4. Beyer, W.: Zentralbl. f. Chir. 68: 1730, 1941.
5. Domagk, G.: Klin. Wehnschr. 21: 448, 1942.
6. Domagk, G.: Deutsche med. Wehnschr. 69: 379, 1943.
7. Heideman, M. L., Jr., and Rutledge, R. C., Jr.: J. Pharmacol. & Exper. Therap. 93: 451, 1948.
8. Rutledge, R. C., Jr., and Heideman, M. L., Jr.: J. PEDIAT. 33: 274, 1948.
9. Knapp, E. L.: Factors Influencing the Excretion of Calcium I. in Normal Persons, J. Clin. Investigation 26: 182, 1947.
10. In preparation.
11. Hartmann, A. F., Perley, A. M., and Barnett, H. L.: J. Clin. Investigation 17: 465, 1938.

REPORT OF A CASE OF POSTVACCINAL ENCEPHALITIS IN A FOUR-MONTH-OLD CHILD WITH RECOVERY

CAPTAIN HERBERT J. JACOBS, CAPTAIN MELVILLE G. MAGIDA, AND
CAPTAIN DAVID R. METCALF, MEDICAL CORPS
ARMY OF THE UNITED STATES

THE purpose of this paper is to report a case of postvaccinal encephalitis in infancy and to review the literature. The authors feel that such a report is of interest inasmuch as this clinical entity is exceedingly rare under one year of age.

To our knowledge this is the first case of a patient under 6 months of age which has been reported in the American literature. Numerous reports of cases in children over the age of one year can be found in American, British, and Continental literature.^{1-19, 36, 37, 41} Flexner²⁰ in 1929 stated that the disease was unknown in this country in children under the age of 6 months; and our review has failed to disclose any additional American cases.

In the foreign journals, however, mention is made of this complication occurring in infants under six months of age. Sakoschansky²¹ refers to the work Hewlett did in 1933 in which that author states that young infants are almost totally immune. Further, he reports a case in a child 14 weeks of age occurring ten days after primary vaccination, mild in character, with recovery. Scott²² in 1932 in his review of British and Continental literature reports twenty-two cases over a five-year period occurring in infants under one year of age. These were collected from British, German, Polish, French, Dutch, and Scandinavian sources; but the data are largely incomplete and inconclusive with regard to diagnostic findings. Thompson²³ states that in England 63 per cent of all vaccinations were done on infants under one year of age. In that age group nine cases of postvaccinal encephalitis occurred. In those vaccinated over one year of age, or 37 per cent, eighty-four cases developed. In Holland he notes that in children under 2 years of age there is an incidence of one case in 13,531 vaccinations (0.002 per cent), while in the 3- to 12-year age group there is an incidence of one case in 3,555 (0.03 per cent).

In American reports, Armstrong²⁴ in 1931 and Hempelman²⁵ in 1936 concurred with the low incidence in infancy.

CASE REPORT

This 4-month-old white male infant was admitted to the Station Hospital on Jan. 31, 1948, with a chief complaint of listlessness of twenty-four hours' duration.

Past History.—The child was normal and full-term, delivered spontaneously as a vertex presentation without instrumentation, after a normal pregnancy. Growth and development were normal. Previous status was unremarkable with no history of contagion. The infant was breast-fed until the age of 3 months, at which time the mother placed him on a formula consisting of evaporated milk, water, and Karo syrup, on which he did well. Immunization for diphtheria-pertussis-tetanus was started (using the alum-precipitated combined preparation of Sharpe and Dohme) at the age of 2½ months. The

full course was completed on January 19 at 3½ months, when vaccination on the left deltoid by the multiple pressure method was performed. Primary reaction developed thereafter with erythema, vesiculation, crusting, and regional adenopathy.

Present Illness.—One week prior to admission (five days after vaccination) the child developed diarrhea characterized by the passage of ten to twelve greenish-yellow, watery stools unassociated with pyrexia or evidence of dehydration. Treatment was symptomatic and the diarrhea subsided after thirty-six hours.

For three days prior to admission (starting nine days after vaccination) the mother noted that the child appeared sluggish, not playful as usual, and manifested occasional vomiting. This persisted until the day before admission, at which time the child became somnolent, did not cry, and would not grasp proffered objects. Later in the course of the day involuntary movements of the left side of the face, corner of the right lip, and roving movements of the eyes were noted. This was associated with "failure to focus," inability to follow objects, and "inward turning" of the left eye. Feeding and bowel habits were normal without evidence of associated systemic reaction or pyrexia. Because of these complaints hospitalization was sought.

Physical Examination.—The child was a well-developed, well-nourished 4-month-old white male, asleep during the examination, crying only with painful stimuli. The skin was clear except for a mild ammoniacal dermatitis of the groins. The anterior fontanel admitted one finger and was under normal tension. Examination of the eyes revealed the pupils to be round, regular, and equal, reacting to light. Objective following of light was absent. Irregular gyrations of the eyes occurred, and paresis of the right lateral rectus and right inferior oblique muscles was noted as manifested by internal strabismus. The ears, nose, and throat were unremarkable. The lungs were resonant and clear to auscultation. The heart was normal in size and configuration with a normal sinus rhythm at a rate of 110 per minute. The abdomen was soft without palpable organs or masses. Neurological examination revealed the neck to be supple. There was no evidence of Kernig or Brudzinski signs. Examination of the cranial nerves revealed them to be intact with the exception of the previously mentioned findings in the right VI and III nerves. The deep tendon reflexes were physiologic, the superficial reflexes active and symmetrical, and the plantar response flexor.

Course.—Lumbar puncture was performed shortly after admission. The dura was entered between L-3 and L-4, the cerebrospinal fluid was found to be under normal pressure, and 8 c.c. of clear fluid were removed. The cell count was 19, 96 per cent of which were lymphocytes and 4 per cent polymorphonuclear neutrophiles. The Pandy reaction for globulin was negative. Total protein was 20 mg. per cent, colloidal gold curve and Wassermann negative.

On admission hemoglobin was 11.6 Gm. (Sahli), red blood cells were 3.88 million, white blood cells were 11,400 with 39 per cent polymorphonuclears, 58 per cent lymphocytes and 2 per cent monocytes.

The findings as noted remained unchanged until the second hospital day (February 2) when the infant experienced the following reaction: coarse twitching of the right frontalis muscle and right upper lid, bilateral rotatory nystagmus, abduction of the right arm associated with contraction of the biceps and rhythmic "pill-rolling" movements of the fingers. The left arm was extended and pronated, and the right leg maintained in extensor spasm with dorsiflexion of the great toe. Respirations were deep and irregular at a rate of 14 to 18 per minute. The tongue was directed to the left, with

coarse fibrillations over its surface. The picture changed intermittently with hyperextension of both upper extremities over the head. The total duration of this episode was forty-five minutes. Blood calcium was 9.2 mg. per cent and carbon-dioxide combining power 52 volumes per cent.

The child for the remainder of the day was afebrile and took nourishment well, though remaining listless and manifesting persistent internal strabismus of the right eye.

On the third hospital day, occasional twitching of the left arm was noted. During the morning feeding, which was poorly taken, paresis of the right upper extremity developed with failure to respond to painful stimuli. The feeding was followed by a paroxysm of coughing and regurgitation. This was rapidly succeeded by drawing up of the left side of the face, and twitching of the nose and left facial muscles. Concomitantly the right lower extremity became rigid, maintained in extensor spasm, and the fingers of the right hand tightly flexed. This was followed by slow, clonic movements of the right lower extremity and rapid, clonic movements of the right hand. The head was turned to the left and rapid, irregular, ocular gyrations were again noted. This episode lasted eight minutes, after which there was no alteration in physical findings.

During the remainder of the hospital course there was no recurrence of a similar nature. By the fifth hospital day the child was alert and active. The right upper extremity was normal in function, ocular gyrations ceased, and internal strabismus of the right eye diminished, while the child regained the ability to follow light in all directions. The child was discharged on the seventh hospital day with minimal residual right internal strabismus. In all other respects the child was normal and active. Temperature never exceeded 100° F. (R) throughout the hospital course, fluctuating between 98.4 and 98.6° F. during the last three hospital days. Therapy was entirely symptomatic.

EPIDEMIOLOGY

A review of the literature^{3, 23, 24, 26, 27, 35} reveals the following pertinent facts. Postvaccinal encephalitis is a complication of primary vaccination, rather than re-vaccination,²⁴ and is rare in infancy.^{12, 20, 21, 22, 24, 25} The type of vaccine used bears no relation to the complication.^{9, 13} The method of vaccination, as well as the degree and character of the local reaction are also apparently unrelated.³⁹ A tendency for grouping of cases as to time and place has been noted.^{9, 23} The incidence of the disease parallels the total number of vaccinations, though is not necessarily proportional.²³ The case rate of postvaccinal encephalitis is lower in the United States than in European countries.^{24, 23}

PATHOLOGY

The pathologic entity has been noted to involve the entire central nervous system,^{26, 34, 39} both white and gray matter, but particularly the former. The characteristic microscopic lesion is perivascular neurone demyelination associated with areas of extra- and intra-adventitial infiltration of leucocytes and glial cells.^{24, 28} The spinal fluid is sterile with a moderate pleocytosis and increased protein. No inclusion bodies have been found.²⁹

In comparing this pathologic reaction with that occurring after measles and the other exanthemata, it has been noted by Greenfield²³ that there is more perivascular infiltration and more complete demyelination in post-vaccinal encephalitis. Further, Thompson²³ states that in encephalitis follow-

ing measles the gray matter is but little affected, while in postvaccinal encephalitis both gray and white matter are involved, though the predominant reaction occurs chiefly in the latter.

PATHOGENESIS

While the pathogenesis of postvaccinal encephalitis is still in doubt, four hypotheses have been postulated: (1) accidental; (2) caused by the virus itself; (3) activation of a latent neurotrophic virus already present; and (4) allergic. The weight of available experimental data indicates that the third theory is most likely.^{23, 28, 30, 31, 32, 33, 40} Rivers³³ supports this view in analogy to the so-called fever blister. The most convincing evidence that the postvaccinal condition is caused by activation of some questionable virus is found in the clinically and possibly pathogenetically similar conditions occurring independently and following other exanthems.

TREATMENT

The results of therapy are inconclusive. An over-all review reveals a gross mortality of approximately 50 per cent with the remainder usually manifesting rapid and complete recovery^{25, 26, 28}. Symptomatic therapy, sulfonamides, and convalescent sera³¹ have not dramatically altered the course of this disease.

SUMMARY

1. A case of postvaccinal encephalitis with recovery in a 4-month-old child is presented.

2. The literature from 1928 to date is reviewed and discussed.

REFERENCES

1. Grose, G.: A Case of Post Vaccinal Encephalitis, *Lancet* 2: 381, 1929.
2. Taylor, J. F.: A Fatal Case of Post Vaccinal Encephalitis, *Lancet* 1: 1302, 1929.
3. Lanim, S. S.: Post Vaccinal Encephalitis: *Am. J. Dis. Child.* 56: 824, 1938.
4. Nunn, J. A., and Magrish, P.: Encephalomyelitis as a Complication of Vaccinia, *Texas State J. Med.* 35: 292, 1940.
5. Andrews, N. S.: Post Vaccinal Encephalitis: *Kentucky Med. J.* 32: 203, 1934.
6. Coyle, C. D., and Hurst, E. W.: A Case Report of Post Vaccinal Encephalitis in a 5-Year-Old Girl, *Lancet* 2: 1246, 1929.
7. Young, R., and Moore, C.: Post Vaccinal Neuronitis, *J. PEDIAT.* 18: 248, 1941.
8. Fulgahm, J. H., and Beykirch, J. G.: Post Vaccinal Encephalitis, *J. A. M. A.* 92: 1427, 1929.
9. Gorter, E.: Post Vaccinal Encephalitis, *J. A. M. A.* 101: 1871, 1933.
10. Miller, M. K.: Four Types of Encephalitis, *J. A. M. A.* 97: 161, 1931.
11. Perritt, R. A., and Carroll, R. C.: Post Vaccinal Myelitis, *J. A. M. A.* 94: 793, 1930.
12. Brockbank, T. W.: Post Vaccinal Myelitis, *J. A. M. A.* 97: 227, 1931.
13. Holbrook, C. S.: Encephalitis and Encephalomyelitis Following Vaccination Against Smallpox: Report of Five Cases, *South. M. J.* 23: 696, 1930.
14. Horder, T.: A Case of Cerebral Symptoms Following Vaccination, *Lancet* 1: 1301, 1929.
15. Gordon, A. H., and Rhea, L. J.: Post Vaccinal Encephalitis, *Am. J. M. Sc.* 184: 104, 1932.
16. Woodward, S. B.: Smallpox and Vaccination, *New England J. Med.* 208: 641, 1933.
17. Roper, F. A.: Encephalitis Following Vaccination With Recovery, *Brit. M. J.* 2: 103, 1933.
18. Dixon, G. J.: Myelitis Due to Vaccination, *J. Neurol. Neurosurg. and Psychiat.* 7: 18, 1944.
19. Dunn, T. M., and Rigdon, R. H.: Post Vaccinal Meningo-encephalomyelitis, *Am. J. Clin. Path.* 11: 771, 1941.
20. Flexner, S.: Post Vaccinal Encephalitis, *Trans. Assoc. Am. Physicians* 44: 181, 1929.
21. Sakoschansky, L., and Trenchard, J. J.: Vaccinal Encephalitis in a Child Aged 14 Weeks, *Brit. M. J.* 1: 1229, 1939.

22. Scott, T. F. McN.: Post Vaccinal Encephalitis in Infancy, *Brit. J. Child. Dis.* 27: 245, 1930.
23. Thompson, R.: The Etiology of Post Vaccinal Encephalomyelitis, *Arch. Path.* 12: 601, 1931.
24. Armstrong, Charles: Post Vaccination Encephalitis, *Ann. Int. Med.* 5: 333, 1931.
25. Hempelman, T. C.: Encephalitis: Clinical Types, Their Symptoms, Diagnosis and Treatment, *Med. Clin. N. America* 20: 415, 1936.
26. Flexner, S.: Post Vaccinal Encephalitis and Allied Conditions, *J. A. M. A.* 94: 305, 1930.
27. Eley, R. C.: The Neurologic Complications of Vaccination, *Harvard Symposium of Public Health*, pp. 226-235, Cambridge, 1940, Harvard University Press.
28. Reisman, H. A., and Utz, D. W.: Post Vaccinal Encephalitis, *Arch. Pediat.* 60: 201, 1943.
29. Viete, H. R., and Warren, S.: Vaccinal Encephalitis: Three Cases, Two With Post-mortem Examination, *New England J. Med.* 204: 475, 1931.
30. Levaditi, C., and Nicolau, S.: A propos de l'etiology de l'encephalite postvaccinial, *Compte Rendu Soc. de Biol.* 94: 114, 1926.
31. Zuriukzoglu, S.: Experimentelle Untersuchungen über Vaccine und Herpes, *Klin. Wechschr.* 6: 70, 1927.
32. Eckstein, A.: Investigations on the Causes of Vaccination Encephalitis, *Arch. Dis. Child.* 7: 105, 1932.
33. Rivers, T. M.: Viruses and Virus Diseases, *Lane Medical Lectures*, p. 60. Stanford University, Calif., 1939, Stanford University Press.
34. Anderson, T., and McKenzie, P.: Post Vaccinal Encephalitis, *Lancet* 2: 667, 1942.
35. Bedson, S. P.: Observations on Vaccination, *Lancet* 2: 920, 1929.
36. Graubart, J.: Post Vaccinal Encephalomyelitis, *Arch. Pediat.* 46: 703, 1929.
37. Burton, A. H. G., and Weir, J. H.: Post Vaccinal and Measles Encephalitis, *Lancet* 2: 561, 1941.
38. Lapage, C. P.: Post Vaccinal Encephalitis in Children, *Brit. M. J.* 1: 811, 1933.
39. Mulligan, R. M., and Neuberger, K. T.: Post Vaccinal Encephalitis in Adults, *J. of Neuropath. and Exper. Neurol.* p. 416, 1942.
40. Madonick, M. J.: Meningoencephalitis Complicating Herpes Zoster Ophthalmicus After Treatment by Vaccination, *Arch. Neurol. and Psychiat.* 56: 434, 1946.
41. Rohmer, P., Saarez, R., and Rohman, J. A.: Study of Five Cases, *Bulletin de L'Academie de Medicin* 131: 60, 1947.

A CASE OF MENINGITIS DUE TO PSEUDOMONAS AERUGINOSA
(BACILLUS PYOCYANEUS) AND NEISSERIA
FLAVESCENS WITH RECOVERY

LIEUTENANT COLONEL RYLE A. RADKE AND CAPTAIN GUY C. CUNNINGHAM,
MEDICAL CORPS, UNITED STATES ARMY

MENINGEAL infections with *Pseudomonas aeruginosa* previously reported have been, in the main, due to involvement secondary to lumbar puncture,^{1, 2, 4} penetrating head wound,³ otitis media¹⁷⁻¹⁹ or have been secondary to invasion of the blood stream from a primary focus in the umbilical cord^{8, 9} or abscess.^{20, 21} Several cases have been reported secondary to intrathecal administration of contaminated materials.^{3, 5-7} Two cases have been reported in which the meningeal involvement appeared to be the primary involvement and not the result of systemic invasion from a recognized focus. Kliewe and Koch¹⁰ reported a case in a 3-year-old child with recovery after eighty days in which the meningeal involvement appeared to be the only recognizable focus of infection, although they suggest that the primary site of infection was stomatitis. Vaughan, Beck, and Shelton¹¹ have reported a second case in a 40-year-old woman who became ill with headaches and in whom the first spinal puncture revealed 1,800 cells and from whose spinal fluid the *Ps. aeruginosa* was cultivated. Blood culture was negative and no primary focus was recognized. In a review of the literature of this subject Evans (1936)¹² reports that she was able to find twenty cases of primary meningeal involvement due to *Ps. aeruginosa*, most of them following lumbar puncture or septicemia. She discovered reports of three cases of infection with this organism in association with other organisms, namely, Friedländer's bacillus, *Mycobacterium tuberculosis*, and staphylococci. In each instance, the infection was secondary to penetrating wound of the skull, otitis media, or lumbar puncture. In her estimate of the literature as recorded the mortality was 66.6 per cent. Those that did recover did so after protracted illness ranging from fifty-four to ninety days. Cairns, Duthie, and Smith¹³ record three cases with fatal outcome treated with streptomycin intrathecally, combined with sulfonamide therapy in one case and sulfonamide and penicillin medication in the other two.

Merworth, Rosenberg, and Pulito²² report a case treated with streptomycin with recovery with residual neurological involvement which was thought to be due to intrathecal streptomycin.

Sarah Branham^{14, 15} reported in 1930 the isolation of *Neisseria flavescens* from a number of cases of meningitis occurring in an epidemic of about forty cases due to the meningococcus. As far as we have been able to determine, it has not been described as causing primary meningitis in association with another organism. The present case to be discussed combined the unusual feature of infection with *Ps. aeruginosa* and *N. flavescens*, both rare organisms in connection with meningitis, particularly primary meningitis with no demonstrable portal of entry into the body.

CASE REPORT

The patient was a 3-year-old, white boy in excellent state of nutrition who had been healthy and normal, until June 4, 1948, at which time his mother

From the Medical Service, Station Hospital, Fort Knox, Ky.

noted that he seemed somewhat less vigorous than usual in his play. On June 5 he refused his lunch and manifested a disinclination to play, complaining of feeling cold and finally having to be carried home. He appeared somewhat drowsy to his parents and refused his supper. His fever was 102° F. He fell asleep but cried out frequently in his sleep and vomited in the early morning of June 6. He was irritable and feverish and vomited again on awakening June 6. About 9:00 AM, June 6 he lapsed into a semistupor from which he could be aroused with difficulty and he was brought to the hospital. He had had no respiratory symptoms, no bowel disturbance other than the vomiting alluded to above, and there were no symptoms referable to the urinary tract. On admission he was irrational and cried out shrilly without external stimulus. Temperature was 101° F. His skin showed residual scars of a recent chicken pox. There were no petechial hemorrhages. His spleen was barely palpable and there was a grade 1 systolic murmur at the mitral area. The eardrums were normal. Kernig's and Brudzinski's signs were present and he had a rigid neck. Lumbar puncture was done and cloudy fluid was withdrawn; 5,000 units of penicillin were injected intrathecally at this time. Smear of this fluid contained numerous gram-negative cocci and diplococci of variable size, a few gram-positive cocci and diplococci of similar morphology and numerous gram-negative bacilli. Sugar was 30 mg. per cent, Pandy 2 plus, cells 980, 95 per cent polymorphonuclear leucocytes. On admission red blood cells were 3.42 million, hemoglobin 11 Gm. white blood cells 9,950, neutrophiles 66 per cent, lymphocytes 32 per cent. A second spinal tap done that same day for the purpose of introducing streptomycin yielded a similar smear. Because of the pleomorphism of the organisms seen in the smear, it was decided to treat the patient with penicillin, 100,000 units every two hours, streptomycin .25 Gm. every three hours, and sodium sulfadiazine .75 Gm. at once intravenously and then 4 Gm. subcutaneously in three divided doses each twenty-four hours. In addition, 15,000 units of streptomycin were introduced intrathecally on the first hospital day and 25,000 units on each of the second and third hospital days. A presumptive diagnosis of influenza bacillus meningitis was entertained at this time, but the penicillin was included because of the baffling nature of the smear of the spinal fluid. Initial spinal fluid culture was reported as showing *Ps. aeruginosa*. Blood culture was negative. Chest x-ray was negative, throat culture reported as showing *Neisseria catarrhalis* as the predominating organism. Spinal fluid culture taken the second day showed growth of *N. flavaescens* and *Ps. aeruginosa* and the smear was similar to the one described above. This specimen had 8,200 cells, 84 per cent polymorphonuclear leucocytes, sugar 16 mg. per cent. Cultures of spinal fluid on the third and sixth hospital days were negative. The course in the hospital was one of steady improvement. He was conscious and able to take nourishment by mouth on the second hospital day and was afebrile on the sixth hospital day. He developed minor convulsions on the third hospital day confined to the face and right arm. All medication was discontinued on the tenth hospital day. When he was discharged from the hospital on the twenty-second day, he had some minor evidences of involvement of the vestibular apparatus. When re-examined thirty days later, there was no evidence of involvement of any nerve, either motor or sensory, his gait and station were normal, and his Romberg was negative.

DISCUSSION

This case represents as nearly as can be determined simultaneous involvement of the meninges with two organisms rarely primarily invasive and without evidence of a primary focus of infection. The smear of the spinal fluid taken on admission contained both organisms and although the *N. flavaescens* was not

recovered from the first specimen culturally, it was readily recovered from the specimen taken the next day and was seen in the first three. No evidence of the gastrointestinal or genitourinary tract being involved was secured and chest x-ray was negative. In retrospect the *N. catarrhalis* found in the throat culture may have been the *N. flavescens*; however, this was not proved. His prompt recovery without residuals is in sharp contrast to the previously described cases of *Ps. aeruginosa* meningitis and is probably due to the fact that his mixed infection made him critically ill in a short time, thus bringing him under treatment very early. It seems likely that the convulsive disorder seen on the third hospital day was a result of intrathecal streptomycin medication, although this cannot be stated categorically. The cases of *N. flavescens* meningitis described by Branham were similar in course to meningococic meningitis, and the onset of this boy's illness is reminiscent of such an illness.

SUMMARY

1. A case of meningitis due to simultaneous invasion with *N. flavescens* and *Ps. aeruginosa* is presented.
2. It is thought that this represents the only reported case of primary involvement of the meninges due to *Ps. aeruginosa* in company with another organism with no injury or portal of entry through infected ear or lumbar puncture.
3. Conversely, it is believed that this is the only reported case of *N. flavescens* invading the meninges in company with another organism.
4. Prompt recovery is attributed to the fact that the fulminating character of the illness brought the patient under treatment very early in the course of the disease.
5. Streptomycin is believed to have played a vital role in the recovery of this patient.
6. Convulsions occurred which were thought to be due to intrathecal streptomycin.

REFERENCES

1. Wise, R. A., and Musser, J. H.: New Orleans M. & S. J. 92: 145, 1939.
2. Beiger, Edmund H.: Northwest Med. 37: 242, 1948.
3. Botterell, E. H., and Magner, D.: Lancet 1: 112, 1945.
4. Levy, I. I., and Cohen, A. E.: J. A. M. A. 85: 1968, 1925.
5. Schneider, Hans: Wien. klin. Wehnschr. 37: 65, 1924.
6. Schlaggenhaufer, F.: Quoted by Evans¹².
7. Shrewsbury, J. F. D.: Brit. M. J. 1: 280, 1934.
8. Benfey, A.: Quoted by Evans¹².
9. Chuan, H.: Centralbl. f. allg. Path. u path. Anat. 38: 483, 489, 1926.
10. Kliwe and Koch: Quoted by Evans¹² and Vaughan, et al¹¹.
11. Vaughan, W. T., Beck R., Shelton, T. S.: Arch. Int. Med. 47: 155, 1931.
12. Evans, F.: Med. Record 144: 111, 1936.
13. Cairns, II, Duthie, and Smith: Lancet 2: 153, 1946.
14. Branham, S. E.: Public Health Rep. 45: 845, 1932.
15. Branham, S. E.: J. Immunol. 23: 49, 1932.
16. Topley and Wilson: Principles of Bacteriology and Immunity.
17. Kossel: Zur Frage der Pathogenität des Bacillus pyocyanus für Menschen, Charite-Ann. 18: 498-504, 1893; Ztschr. f. Hyg. 16: 368, 1894.
18. Horder: Bacillus Pyocyanus Meningitis of Otitic Origin, Trans. Path. Soc. London 55: 141-142, 1904.
19. Traenkel, E.: Ueber die Menschenpathogenität des Bacillus pyocyanus, Ztschr. f. Hyg. u. Infektionskr. 72: 496-520, 1912.
20. Berka, F.: Pyocyanusbefund bei Meningitis, Wien. klin. Wehnschr. 16: 308-310, 1903.
21. Hubener: Ein Fall von Pyocyanussepsis beim Erwachsenen, Deutsche med. Wehnschr. 33: 803-804, 1907.
22. Merworth, H. R., Rosenberg, M., and Pulito, F.: Brooklyn Hosp. J. 5: 93-98, 1947.

Clinical Conference

CONFERENCE AT THE CHILDREN'S MEMORIAL HOSPITAL OF CHICAGO

DR. J. A. BIGLER AND DR. STANLEY GIBSON

Case 1. Congenital Dermal Sinus

DR. LEININGER.—Chief complaint: Prolonged intermittent fever; irritability.

We are presenting the case of a 22-month-old white male infant who apparently had enjoyed good health up until the present illness, which dates back to the third week in May, 1948, when a small dimple over the lumbar area of the back began to discharge a thin, yellow material. This continued on and off until July, 4, at which time the father observed that there was no longer any discharge present. That evening the child vomited and was found to have a rectal temperature of 102° F. The next morning he developed generalized malaise and his fever persisted. He was seen by a pediatrician in Grand Rapids, Mich., and the parents were told that he had a mild infection of the throat and ears. The following day he seemed somewhat improved; however, on July 7 he was more irritable and his temperature again rose to 102° F. On the eighth day of July he was admitted to Butterworth Hospital, Grand Rapids, Mich., because of stiffness of the neck. A lumbar puncture was performed and the spinal fluid was cloudy with 1,584 cells, 90 per cent of which were polymorphonuclear leucocytes. The sugar was 35 mg. per cent. The Pandy was one plus. No growth was obtained upon culture. Urinalysis was negative. The red blood count was 4,400,000 per cubic millimeter. The differential revealed 74 per cent neutrophiles, 8 per cent lymphocytes, and 18 per cent monocytes. Penicillin 100,000 units every three hours, streptomycin 25,000 units every three hours, and adequate doses of sodium sulfadiazine were instituted. The penicillin and streptomycin were discontinued after one week of therapy. His progress while in the hospital was uneventful except for occasional spikes of fever during the first week. He was finally discharged from the hospital July 28 with a spinal fluid which showed a cell count of 62, 80 per cent of which were neutrophiles, and a sugar of 39 mg. per cent. He was asymptomatic until two days later, when he again became quite irritable and his temperature rose to 102° F. Because of continued elevation of temperature he was readmitted to the hospital on August 2, at which time spinal fluid examination revealed 1,320 cells, 40 per cent of which were neutrophiles, and a one plus Pandy. The complete blood count was essentially unchanged. He was given glucoseulfadiazine, streptomycin, and penicillin. He continued to run an intermittent, febrile course but was not drowsy and only slightly irritable. There was a mild stiffness of the neck and back. On August 5 a lumbar puncture revealed 900 cells, 60 per cent of which were neutrophiles, and a one plus Pandy. X-rays of the mastoids were negative.

A tuberculin test (1:1,000 O. T.) was negative. Urinalysis was negative. Because of the persistent, low-grade, otitis media which seemed to be present, an otolaryngologist was called in concerning the advisability of a bilateral myringotomy. He did not feel that the procedure was indicated. A neurosurgeon had been consulted concerning the dimple in the skin over the lumbar area and its possible relationship to his present illness. He believed that a pilonidal sinus was present and that it had no relationship to the meningitis.

On admission the child appeared surprisingly well in view of his illness for the past month. The only positive findings upon examination were mild irritability, a slightly stiff spine, and apparently mild pain upon flexion of the neck; however, there was no actual nuchal rigidity. The Kernig and Brudzinski signs were negative. Fundoscopic examination revealed no papilledema. Both tympanic membranes appeared slightly reddened but there was no bulging, perforation, or discharge.

A lumbar puncture was performed and a cloudy fluid containing 638 cells, 90 per cent neutrophiles, was obtained. The Pandy was one plus. The protein was 37 mg. per cent, the sugar 38 mg. per cent, and the chlorides 749 mg. per cent. Anaerobic and aerobic cultures were taken. No growth was obtained on the latter but Brewer's thioglycollate media revealed a growth of gram-negative, pleomorphic bacilli showing bipolar staining. Attempts to subculture this organism were unsuccessful and a Quellung reaction was negative. Complete blood count was essentially the same as before except that there was now a milk leucocytosis (16,300 per cubic millimeter). Urinalysis was negative.

The child was placed on a general diet and specific therapy, consisting of 125,000 units of streptomycin subcutaneously every three hours, 30,000 units of penicillin every three hours, and 1.5 grains of sulfadiazine per pound of body weight per day in divided doses every four hours.

X-rays of the skull and mastoids were reported as normal. Dr. George S. Livingston examined the child and believed that the initial ear infection could have been responsible for a serous meningitis, which would explain the absence of pyogenic organisms in the cerebrospinal fluid. He doubted the presence of a brain abscess and felt that the significance of the sinus over the lumbar area should be evaluated by Dr. Douglas N. Buchanan. Dr. Buchanan reviewed the history and examined the child on August 11, at which time he observed that the sinus was present in the center of a small, flat hemangioma. He pointed out that this sinus was over the area of L₅, rather than lower down in the usual region of a pilonidal sinus. His diagnosis was congenital ectodermal sinus with probably a deep abscess, and he felt that the recurrent meningitis was unquestionably a complication of the dermal sinus. He recommended that a neurosurgeon remove the dermal sinus in its entirety after the present infection had subsided completely. Because of the nature of the illness, he prognosticated that in spite of continued adequate therapy, recovery would be quite slow.

Upon his suggestion, the therapy which had been instituted at the time of admission was continued and spinal fluid examinations were obtained at weekly intervals. On August 16 the spinal fluid contained, 1,510 cells, 94 per cent of which were neutrophiles. The previous results were once again obtained upon

attempting to culture the organism. The protein was 102 mg. per cent, sugar 24 mg. per cent, chlorides 696 mg. per cent. On August 23 another spinal tap revealed 1,020 cells, 96 per cent of which were neutrophiles. The protein was 96 mg. per cent; sugar 22 mg. per cent; and the chlorides 699 mg. per cent. No organisms were obtained upon cultures. A specimen of the original organisms cultured has been sent to the Illinois State Public Health Laboratory; however, no report has been received up to the present time.

While in the hospital the patient followed a fairly uneventful course. He was occasionally irritable but never manifested a cerebral cry or pronounced nuchal rigidity. Fundoscopic examination continued to be negative and no localizing signs attributable to a space-occupying cranial lesion were ever observed. In spite of the prolonged streptomycin therapy he had shown no evidence of eighth-nerve irritation or deafness. He had a fairly good appetite during his stay in the hospital and gained two pounds in a period of three weeks. An interesting feature of his course in the hospital was his temperature curve. In spite of fairly high doses of penicillin, streptomycin, and sulfadiazine, he continued to have an intermittent, spiking fever (up to 103° F.), usually once a day.

Dr. Buchanan was consulted August 24. The temperature curve and the most recent spinal fluid findings were described to him. He believed that the present therapy was adequate in dosage and method of administration and that continued therapy would be necessary for at least four to six weeks more. In view of the fact that there were adequate hospital facilities and professional care, including a neurosurgeon, in Grand Rapids, Mich., he recommended that the child be transferred back to Butterworth Hospital for continued care and final treatment of the present illness. Such arrangements were made with the referring pediatrician and the child was discharged Aug. 25, 1948. His further progress will be reported to us at a later date.

This is the fourth case of congenital dermal sinus which has been observed at Children's Memorial Hospital, two of the previous cases having been reported by Walker and Buey in 1934 following surgery at Bobs Roberts Hospital. The other unreported case at this hospital is that of a child who has not yet been discharged and who is receiving treatment by the orthopedic department for multiple congenital orthopedic anomalies. She was first seen at one year of age, at which time her presenting symptoms were paresis of the left leg and paralysis of the right leg. A diagnosis of myelodysplasia (T_6-S_2) and a congenital dermal sinus at L_2 was made. Surgical excision of the sinus was recommended at a later day; however, shortly thereafter she developed an influenzal meningitis which was treated successfully with streptomycin for seven days and sulfadiazine for fourteen days. Surgical excision has been deferred since, because the advisability of such a procedure has been questioned in view of the extensive myelodysplasia. At the present time the child has paresis of the left leg, paralysis of the right leg, and fecal and urinary incontinence.

Congenital dermal sinus is a relatively rare condition, as manifested by the fact that most of the pediatric textbooks and texts on pediatric neurology devote

usually less than one-half page to a complete discussion of this medical entity. A review of the literature also reveals that only nineteen such cases have been described. Table I lists these cases, the age at which the disease was first observed, and the level at which the dermal sinus entered the vertebral column.

TABLE I*

AUTHOR	LEVEL	AGE
Clark (1918)	C4	13 years
Moise (1926)	S1	18 years
Ripley and Thompson (1928)	S2	3½ months
Sharpe and Sharpe (1928)	T11	3 years
Ottomello (1933)	T3	20 years
Hipsley (1933)	T1	3 years
Walker and Bucy No. 1 (1934)	T4	5 years
Walker and Bucy No. 2 (1934)	L4	3 years
Walker and Bucy No. 3 (1934)	L5	3 years
Hamby (1936)	L3	20 years
Stammers No. 1 (1938)	S1	2 years
Stammers No. 2 (1938)	S4	4 years
Boldrey and Elvige (1939)	L5	2½ years
Kooistra (1942)	T3	19 years
O'Connell (1942)	L4	4 years
Shenkin, Hunt and Horn (1944)	S2	2 years
Waring and Pratt-Thomas No. 1 (1945)	L5	10 years
Waring and Pratt-Thomas No. 2 (1945)	L3	16 months
Cliffton and Rydell (1947)	S2	22 years

*From Cliffton, Major E. E., and Rydell, Lt. J. R.: Congenital Dermal (Pilonidal) Sinus With Dural Connection, *J. Neurosurg.* 4: 280, 1947.

Walker and Bucy (1934) pointed out that although pilonidal sinus was a relatively common occurrence, the instances in which a connection with the subdural or subarachnoid space was demonstrated, either at surgery or by clinical signs of localized abscess or meningitis, were relatively uncommon. By referring to the above table it can be seen that there have been only six such cases where a sacrooccygeal sinus was present. In significant contrast to this observation is the fact that such a communication has been demonstrated in all reported cases of congenital dermal sinus of the lumbar, thoracic, or cervical areas. The most commonly encountered complication of a congenital dermal sinus has been a subdural or subarachnoid abscess with resultant neurologic findings due to pressure and adhesions (paraesthesia, paralysis, fecal and/or urinary incontinence). Meningitis has occurred in at least eight of the previously reported cases (Moise, 1926; Ripley and Thompson, 1928; Walker and Bucy, 1934; Stammers, 1938; O'Connell, 1942; Shenkin, Hunt, and Horn, 1944; Waring and Pratt-Thomas, 1945). Recurrent meningitis has been observed in several instances, and for this reason the possibility of a congenital dermal sinus should be considered in any case where a child has suffered from recurrent attacks of meningitis.

Clinically, the diagnosis of congenital dermal sinus has seldom been made prior to the onset of symptoms due to a complicating infection; however, if one is aware of this medical entity and thorough in all routine physical examinations, the diagnosis can be made in an otherwise apparently normal child. The sinus usually lies in the midline of the back and is discernible on the surface of the skin as a tiny dimple, pinpoint in size, which usually lies in the center of a

small area of pigmentation. At surgery the sinus is observed to course perpendicularly to the skin through the soft tissues as an ectodermal tube 3 to 10 mm. in diameter. Its course continues through a bony defect in the vertebral column, usually at a point cephalad to the skin dimple. A spina bifida occulta, therefore, is usually observed (only one case has been reported where a spina bifida occulta was absent, Walker and Buey, 1934). The skin dimple can best be demonstrated by examining it through a plus 8 lens of an ophthalmoscope. The diagnosis of congenital dermal sinus can, therefore, be made upon the observation of a tiny skin dimple in the midline of the back over the lumbar, thoracic, or cervical area, with concomitant spina bifida occulta.

The origin of congenital dermal sinus and its relationship to pilonidal sinus are controversial issues. Previous investigators have suggested that sacrococcygeal sinuses, or so-called pilonidal sinuses, arise from the vestiges of the medullary canal (Herrmann and Tourneux, 1887; Mallory, 1892; Gage, 1935-36; Oehlecker, 1926; Weeder, 1933; Shenkin, Hunt and Horn, 1944; and Cliffton and Rydell, 1947). Walker and Buey (1934) point out that such an origin is not conceivable in dermal sinus occurring in the higher segmental levels, and that some other explanation must be given. They conclude that at the time when the cutaneous-epithelial ectoderm and the neuroepithelial ectoderm should have separated (first month of intrauterine life), the cleavage between them was incomplete at the particular point where the sinus occurred; thus the neural tube carried down with it a narrow invagination of the skin, clothing it with a mesodermal covering continuous with its own connective tissue covering, the meninges. Whether this same explanation of the etiology is true for pilonidal sinus is a matter for conjecture, but it is at least a possibility (Fere, 1878; Stone, 1924; and Fox, 1935).

DR. GIBSON.—Do these cases all have meningitis?

DR. LEININGER.—Eventually, yes. The first symptoms may be due to abscess formation at the end of the sinus with pressure symptoms. Findings of a sterile or serous meningitis may be present, but eventually all patients will develop a bacterial meningitis.

DR. BIGLER.—Should a dermal sinus be removed surgically as soon as detected, even in the absence of symptoms?

DR. BUCHANAN.—Yes, because of the fact that we feel that infection eventually complicates any case of dermal sinus. Surgical removal is much simpler before this complication has arisen.

REFERENCES

- Cliffton, Major E. E., and Rydell, Lt. J. R.: Congenital Dermal (Pilonidal) Sinus With Dural Connection, *J. Neurosurg.* 1: 276-282, 1947.
Fere, C.: Cloisonnement de la cavite pelvienne; uterus et vagin doubles; infundibulum cutane de la region sacro coccygienne, *Bull. Soc. Anat. Paris* 53: 309-312, 1878.
Ford, Frank, R.: Diseases of Nervous System in Childhood and Adolescence, Springfield, Ill., 1944, Charles C Thomas, Publisher.
Fox, S. L.: The Origin of Pilonidal Sinus With an Analysis of Its Comparative Anatomy and Histogenesis, *Surg., Gynee., & Obst.* 60: 137-149, 1935.

- Gage, M.: Pilonidal Sinus: An Explanation of Its Embryological Development, *Arch. Surg.* 31: 175-180, 1935.
 Gage, M.: Pilonidal Sinus, *Internat. Clin.* 3: 19-32, 1936.
 Herrmann, G., and Tourneur, F.: Les vestiges du segment caudal de la moelle épinière et leur rôle dans la formation de certaines tumeurs sacro coccygiennes, *D. R. Acad. Sc., Paris* 104: 1324-1326, 1887.
 Mallory, F. B.: Sacro coccygeal Dimples, Sinuses, and Cysts, *Am. J. Med. Sc.* 103: 263-277, 1892.
 Moise, T. S.: Staphylococcus Meningitis Secondary to a Congenital Sacral Sinus, with Remarks on the Pathogenesis of Sacro Coccygeal Fistulae, *Surg., Gynec., & Obst.* 42: 394-397, 1926.
 O'Connell, J. E. A.: Proc. Roy. Soc. Med. 35: 685, 1942.
 Oehlecker, F.: Sakralabszesse bei kongenitalen Hautverlagerungen (bei sogenannten Dermoidfisteln, bei Foveae sacro coccygeae, Eckerschen Fisteln oder kaudalen Rückenmarkresten), *Dtsch. z. Chir.* 197: 262-279, 1926.
 Ripley, W., and Thompson, D. C.: Pilonidal Sinus as a Route of Infection in a Case of Staphylococcus Meningitis, *Am. J. Dis. Child.* 36: 785-788, 1928.
 Shenkin, H. A., Hunt, A. D., Jr., and Horn, R. C., Jr.: Sacro coccygeal Sinus (Pilonidal Sinus) in Direct Continuity With the Central Canal of the Spinal Cord, *Surg., Gynec., & Obst.* 79: 655-659, 1944.
 Stammers, F. A. R.: Spinal Epidural Suppuration, With Special Reference to Osteomyelitis of the Vertebrae, *Brit. J. Surg.* 26: 366-374, 1938.
 Stone, H. G.: Pilonidal Sinus (Coccygeal Fistula), *Ann. Surg.* 79: 410-414, 1924.
 Walker, A. E., and Bucy, P. C.: Congenital Dermal Sinuses: A Source of Spinal Meningeal Infection and Subdural Abscesses, *Brain* 57: 401-421, 1934.
 Waring, J. I., and Pratt Thomas, H. R.: Congenital Dermal Sinus as a Source of Meningeal Infection, *J. PEDIAT.* 27: 79-83, 1945.
 Weeder, S. D.: Pilonidal Cyst, Its Etiology and Treatment, *Ann. Surg.* 98: 385-393, 1933.

Case 2. Infectious Hepatitis

DR. LEININGER.—Chief complaint: large abdomen; yellow skin.

This child was born Sept. 26, 1947, was admitted to the Children's Memorial Hospital on July 20, 1948, and died on July 28, 1948.

This 10-month-old female infant of Jewish extraction was apparently well until three or four weeks prior to admission, when the parents noted that her abdomen was getting progressively larger. During this time she acquired a dark yellowish tinge to the skin and was somewhat apathetic. Her urine became unusually yellow and sometimes almost greenish-yellow. She was having approximately two bowel movements a day and these were foul-smelling, light cream in color, foamy, and well-formed. She vomited on three or four occasions but this consisted only of ingested food and there was no bile or blood observed. The patient was seen by Dr. Alfred Traisman, who advised admission to the hospital for investigation.

Past history revealed a normal pregnancy and a normal full-term delivery. She weighed 6½ pounds at birth. She had been in good health except for occasional colds. Development was slightly delayed in that at 10 months she could not sit by herself and no teeth were present. She received her whooping cough immunization at 7 and 8 months of age and her diphtheria-tetanus at 9 months. There was no history of exposure to phenol, benzol, or persons ill with jaundice. The family history was essentially negative.

Physical examination upon admission revealed a well-nourished but only fairly well-developed, mildly jaundiced, female infant, in no acute distress. The only other positive findings were noted on examination of the abdomen. It was distended, but there was no evidence of a fluid wave. The liver was

down two fingerbreadths and the spleen was questionably palpable. The diagnostic impression was obstructive jaundice.

On July 22 small, round, hard, movable nodes were felt in both inguinal regions and in the axillae. The liver seemed larger and more tender. The jaundice was more pronounced. The patient went downhill gradually and on July 22 she was dyspneic and stuporous. Oxygen, intravenous fluids, and penicillin were administered. Later that day the child went into coma and had an emesis of coffee-ground material. Twitching and carpopedal spasms were noted, for which calcium gluconate and blood were administered. The respirations became even more labored and numerous ecchymotic areas were noted. The patient expired the following day. Fever was present only terminally and while in the hospital she received only one transfusion, consisting of 70 c.c. of compatible blood on July 27.

Laboratory examinations.—Laboratory examinations revealed the following:

Blood: On July 21, hemoglobin was 12.5 Gm.; red blood cells 4,300,000; white blood cells 11,400; platelets 218,000. Differential count was polymorphonuclears, segmented 23, stabs 5; lymphocytes 71; monocytes 1; reticulocytes 4.5 per cent. July 27 hemoglobin was 10.8; red blood cells 3,490,000; white blood cells 29,750; platelets 238,000. Differential was polymorphonuclears segmented 6, stabs 5; lymphocytes 19; monocytes 12, atypical lymphocytes 58. Coagulation time was 3½ minutes (normal 2 to 4). Bleeding time 2½ minutes (normal ½ to 3). Tourniquet test was negative.

Blood Wasserman and Mantoux 1-1,000 were negative.

Bone marrow biopsy done on July 26 showed that the predominant cell was an abnormal marrow constituent. "It suggests a malignancy which has invaded the bone marrow." (Dr. Pierce.)

Blood chemistry on July 23 showed an icteric index of 71 (1 to 6 normal); cholesterol 316 (150 to 230 normal); cephalin flocculation 4 plus (normal 0) and on July 26 icteric index was 108, cholesterol 308. Van den Bergh gave an immediate direct reaction and an indirect positive strong. Heterophile agglutination was 1/32.

Urinalysis on July 20 showed bile 2 plus, but otherwise was negative. Benzidine was negative. Culture showed *Escherichii coli*. Urobilinogen 1.2 mg. per 100 c.c. (normal 0 to 8 mg.).

Stool on July 20 showed urobilinogen 1 plus (normal 1 to 3 plus); unchanged bilirubin 0 (normal 0); benzidine negative.

Radiologic report July 20 showed that flat plate of the abdomen was negative. On July 21, the chest was negative but the abdomen suggested the presence of fluid. On July 23 an intravenous pyelogram was negative.

DR. PEDVIS.—The major problem in this case was to discover the etiology of the jaundice. Hence we will begin this discussion by reviewing some of the more recent information on this subject.

Jaundice may be defined as a discoloration of the body tissues and fluids by bile pigment. The liver cells help to form bile which is made up of bile salts, bile pigment, cholesterol, mucus, mineral salts, lipid fractions, and urea. We are primarily interested in the bile pigment-bilirubin which is the cause of jaundice. Bilirubin is derived from hemoglobin. Hemoglobin is made up of 4 per cent heme, which is a ferrous complex of protoporphyrin, and 96 per cent

globin. It is taken up from the blood by phagocytic cells which are anchored within the capillaries of the liver, spleen, and bone marrow—reticuloendothelial system, where it is split. Oxidation occurs and the ring opens with the formation of verdohemoglobin. Verdohemoglobin is actually a biliverdin-iron-globin complex. The iron is split off and travels in the globulin fraction of the plasma, leaving the bilirubin globin which remains with the serum albumin. The globin remains attached to the bilirubin until it passes through the liver cells, where the latter is converted into sodium bilirubinate and is excreted into the bile canaliculari with the rest of the bile. Bilirubin globin exhibits a delayed or indirect Van den Bergh reaction and is not excreted in the urine, whereas sodium bilirubinate exhibits a prompt Van den Bergh and is readily excreted in the urine. When the bile reaches the duodenum the bilirubin is reduced by bacteria to mesobilirubinogen and to stercobilirubinogen. These together are known as urobilinogen. The former on exposure to air is oxidized to urobilin 9 alpha, the latter to stercobilin. These two collectively are known as urobilin.

The urobilinogen is either¹ excreted in the feces as urobilinogen, or² re-absorbed from the intestine into the blood stream where it is either^a conducted to the liver and re-excreted in the bile or^b conducted to the kidneys and excreted in the urine.

Various methods have been used for estimating the amount of bile pigment in the body fluids. The Van den Bergh reaction is probably the best known of these and has formed the basis of several classifications of jaundice. In the older qualitative method of doing the test four types of reaction can occur: (1) immediate direct—this measures the direct reacting bilirubin, that is, the sodium bilirubinate; (2) delayed (30 seconds to 2 hours)—this measures the indirect reacting bilirubin, that is, the bilirubin globin; (3) Biphasic (immediate color gradually deepening)—this measures the direct and indirect bilirubin; (4) Negative—no bilirubin is present.

The newer, quantitative method of doing the Van den Bergh test is a photoelectric method. The first part of the test measures total bilirubin, that is, sodium bilirubinate and bilirubin globin. The second part of the test measures the direct or sodium bilirubinate. In order to get the indirect type, bilirubin globin, one subtracts the latter from the former. This method gives accurate figures and also has the added advantage that the D (direct) over T (total) ratio is instructive, 70 per cent usually being found in the obstructive type of jaundice, 15 per cent in the hemolytic type, and 40 per cent where liver damage occurs with impaired excretion and obstruction.

The delayed or indirect reaction measures the bilirubin which the liver has failed to remove from the blood, that is, bilirubin globin. The immediate or direct reaction measures the bilirubin which has passed through the liver cells into the bile canaliculari and which has subsequently found its way back into the blood because of obstruction of duets or necrosis of liver cells. This is sodium bilirubinate and in this case the whole bile containing bile acids and cholesterol as well as the bilirubin has been regurgitated into the blood.

With the true direct reaction in the blood it is found that the urine contains bilirubin and may contain bile salts as well. This is because the sodium bilirubinate is unbound and, therefore, can pass through the kidneys.

With the indirect reaction there are no bilirubin or bile acids present in the urine; however, there is an increase in urobilinogen. This is due to the fact that the bilirubin globin is bound to plasma protein and so cannot pass through the kidney filter. The urobilinogen is increased (1) because more bilirubin is excreted to the intestine and so more urobilinogen is formed and subsequently is absorbed back into the blood and (2) because there is subnormal function of the liver and it therefore removes less urobilinogen from the blood to be re-excreted in the bile.

With the direct reaction in the blood the fecal urobilinogen is decreased because the liver has difficulty excreting the bilirubin into the intestine. With the indirect reaction the fecal urobilinogen is increased because there is an increased production of bilirubin and hence an increased formation of urobilinogen in the intestine.

The icterus index is a useful guide in following patients with jaundice; however, it has the disadvantage that it measures the presence of any pigment in the blood, not only bilirubin.

Rich has suggested the following classification of jaundice:

1. *Retention Jaundice*.—This is due to the overproduction of bilirubin combined with subnormal liver function due to various causes. The liver shows cloudy swelling and atrophy but there is no necrosis or blocking of duets. The blood shows an indirect Van den Bergh reaction. There is an increase of urobilinogen in both the urine and stool.

2. *Regurgitation Jaundice*.—This is due to the rupture of bile canaliculi from various causes. The liver shows necrosis of cells and obstruction of bile duets. The blood shows a direct Van den Bergh reaction. The urine shows an increase in bilirubin and bile salts but a decrease in urobilinogen. There is a decrease of urobilinogen in the stool.

If one now considers the data presented with regard to the case of M. L. B., it is apparent that this was primarily a regurgitation type of jaundice. Furthermore, all of the possible causes of regurgitation jaundice can be easily ruled out with the exception of infectious hepatitis, acute yellow atrophy, and tumors of the liver. The following brief review of the latter conditions may help to clarify the problem.

Epidemic catarrhal jaundice and nonspirochetal jaundice became known as infectious hepatitis in 1937, when it was realized that the infection is localized in the liver rather than in the duodenum and large bile ducts. The term *homologous serum jaundice* is used to refer to hepatitis artificially acquired from any cause. The clinical picture is the same as in infectious hepatitis; however, the incubation period is longer in serum jaundice, and having one of these does not give immunity to the other. Furthermore, the stools are infective only in infectious hepatitis. It is probable that there are two types of hepatitis virus which are closely related. At the present time homologous

serum jaundice includes cases acquired after the administration of yellow fever vaccine, measles antiserum, mumps, convalescent serum, and transfusions.

The etiologic agent in this disease is a specific virus; however, it has not been grown in the laboratory.

A susceptible person acquires the condition from a patient with the disease, probably by droplets, contaminated food, or water. The possibility of non-icteric patients as potential carriers is being explored.

The onset of the disease may be grippelike in nature or consist chiefly of gastrointestinal symptoms of an abrupt or gradual nature. In children, apathy, listlessness, and drowsiness are very common. Usually the first signs are bile in the urine, followed by yellow sclerae and yellowness of the skin which last about two weeks. If the clinical picture of hepatitis persists for more than three weeks, one should reconsider the diagnosis or think of irreversible changes in the liver which are going on to acute yellow atrophy. In addition, there are frequently anorexia, vomiting, abdominal pain, diarrhea, gray-colored stools, headache, fever, central nervous system symptoms, backache, and edema. On examination one notes the jaundice, the enlarged liver, and occasionally an enlarged spleen.

Laboratory findings usually reveal a white blood count which ranges from 10,000 to 12,000 and falls to 8,000 with a relative lymphocytosis. The liver function tests vary. The Van den Bergh is direct at first, then diphasic as recovery begins, and in the terminal phase of recovery is indirect. The urinary urobilinogen is increased at the onset of the jaundice, then disappears when complete regurgitation of bile occurs, only to reappear again with recovery. The urobilinogen is decreased in the stools.

The prognosis in this condition is good. The mortality is 0.1 per cent to 1 per cent.

Acute yellow atrophy is caused by various toxic agents including the heavy metals, mushroom poisoning, and infections. Clinically the picture is very similar to infectious hepatitis except that the patients' jaundice and symptoms become rapidly worse and they die within a short time.

The tumors of the liver can be divided into two groups, primary and secondary. In the primary type, the benign variety are usually very slow-growing and the malignant equally rapid. The latter may show evidence of local and generalized spread. In the secondary type, neuroblastomas are the commonest, and here one has the signs of the original lesion.

With the above possible diagnoses in mind, we will now go on to a description of what was actually found at post-mortem examination.

SUMMARY OF PATHOLOGY

The body was that of a fairly well-developed but poorly nourished white female infant with dark yellowish discoloration of the skin, sclerae, and mucous membranes. On internal examination all the viscera showed a yellowish discoloration.

There was a moderate, generalized lymphadenopathy and microscopically the lymph nodes were hyperplastic and congested.

Both lungs showed only scattered hemorrhages but microscopically there was evidence of passive congestion and scattered areas of atelectasis.

The spleen was moderately enlarged, weighing 34 Gm. (normal 22). It was purplish-red in color, smooth, and firm in consistency. On cross-section it appeared normal. However, microscopic examination showed evidence of passive congestion.

The intestine was filled with a dark brownish-black material which was probably indicative of hemorrhage; however, the mucosa appeared normal.

The organ which showed the most marked changes and the one which interested us most was the liver. It weighed 344 Gm. (normal 274). On gross examination it was noted to be enlarged, reddish-brown in color, smooth, and firm in consistency, except for two small areas, one in the right lobe and the other in the left lobe of the liver; these were yellow in color and firmer in consistency than the remainder of the liver. On cross section the latter areas were very light brown in color, homogeneous, and fairly well-demarcated from the surrounding parenchyma. The parenchyma was pinkish-brown in color and the lobulations could not be made out distinctly.

The gall bladder and the biliary ducts appeared normal.

On microscopic examination of the red areas, or the so-called normal-looking parts of the liver, it was noted that the liver cells had disappeared completely, but the lobules could still be outlined by proliferating ducts. The sinusoids were present and greatly engorged. The reticulum framework of the lobules was not destroyed and throughout there were scattered numerous, inflammatory cells and macrophages. This was the result of a destructive process, the entire lobules throughout large areas of the liver having been reduced to skeletal frames. Here, where the inflammatory reaction is so evident, is where the name *hepatitis originated*. These changes begin in the central part of the lobule and any fragment of hepatic parenchyma that still remains is found in the peripheral zone. In the area of destruction some of the inflammatory cells have engulfed small granules of yellow pigment (lipofuscin). It is probably a normal pigment of the liver cells which is liberated and rapidly phagocytosed when these cells disintegrate. This serves as an indicator of breakdown of hepatic parenchyma. The rapid cell destruction and removal of the debris is very characteristic of this type of atrophy and distinguishes it from those caused by heavy metals and poisons, where there is evidence of cell death.

In the nodular yellow areas the tissue was in a state of regenerative hyperplasia. The hepatic cells had been formed but the architectural pattern only rarely approached the normal. It began with the presence of binucleated or multinucleated liver cells extending from the remaining portions of hepatic columns into depleted stroma. The marked degree of ischemia of the hyperplastic tissue stood out in contrast to the great engorgement of the tissue in the areas of red atrophy. Beside the regenerative changes in the liver cells there were proliferative changes in the bile ducts, especially in the septal ducts.

During the last war Lucke had the opportunity to study 125 cases of fatal epidemic hepatitis. He was able to show that idiopathic yellow atrophy represents the extreme lesion of epidemic hepatitis and, further, that this yellow atrophy differs anatomically from the yellow atrophy caused by heavy metals and other chemical agents, that of eclampsia, and that of a number of bacterial infections.

The pathologic lesions described in the case of M. L. B. are typical of those seen by Lucke. Furthermore, the clinical picture and laboratory findings which he found in the reviewing of his cases are also very similar. This proves undoubtedly that we were dealing with a case of hepatitis that went on to yellow atrophy.

The next problem was to determine where this child contracted her disease. Homologous serum jaundice was ruled out by the fact that she had not received any convalescent sera or transfusions prior to her illness. Hence she must have contracted infectious hepatitis from a carrier, who to this date remains undiscovered.

DR. BIGLER.—Why was the urobilinogen level quoted within normal limits?

DR. PEDVIS.—In this type of jaundice the obstruction is not complete and therefore some sodium bilirubinate can get through to the intestines where it is converted into urobilinogen and therefore appears in the stools. Some of the urobilinogen is reabsorbed and so again a small amount appears in the urine.

DR. BIGLER.—How do you differentiate between infectious hepatitis and acute yellow atrophy?

DR. PEDVIS.—The course in yellow atrophy is much more rapid, all the functions of the liver are depressed to very low levels, and tyrosine is found in the urine.

DR. BIGLER.—Is choline or methianine of value in the treatment of this condition?

DR. PEDVIS.—A recent review in the bulletin of the Johns Hopkins Hospital concludes that these substances are only of questionable value in the treatment of chronic liver disease.

REFERENCES

- Lucke, B.: Am. J. Path. 20: 471, 1944.
Mitchell and Nelson: Text Book of Pediatrics, Philadelphia, W. B. Saunders Co.
Rich, A. R.: Johns Hopkins Bull. 47: 338, 1930.
Watson, C. J.: Blood 1: 99, 1946.
Young, L. E.: New England J. Med. 237: 255, 1947.

Case 3. Barbiturate Poisoning

DR. LEININGER.—Chief complaint: headache, staggering gait, coma.

We are presenting the clinical history of a 10-year-old boy who was admitted to Children's Memorial Hospital in a comatose condition and whose illness, according to the history obtained from the parents, apparently began one month ago. The onset and course up to two days before admission was marked by frontal headache without nausea or vomiting. There had been no particular localization of this headache to the right or left side. The headaches had been frequent in occurrence, had been rather severe in character, but had usually been relieved by aspirin and sleep. At no time had the patient complained to his parents of symptoms which could be ascribed to the aura of a migraine attack. Apparently no ataxia had been present or at least observed during the above period. However, two days before admission he was scuffing in bed with his father when he suddenly complained of dizziness and went to

his room. He stated that he had a "funny feeling in his head." At this time he did not complain of nausea or vomiting, but he had no desire to eat. He slept until 5:00 P.M. and then came downstairs where he was observed by his parents to stagger and bump into chairs. They seemed to feel that he had a tendency to veer forward and to the left. He was helped back upstairs and was placed in bed. At this time he complained of diplopia. He slept restlessly through the night and had to get up three times to go to the bathroom. On each occasion it was necessary for his father to assist him because of his staggering gait. The following morning he seemed somewhat improved but his eyes "didn't look right." He seemed to hold his head back and looked out from beneath half-closed eyelids with a vacant stare. His parents described his appearance as that of an individual peering through the near-vision lenses of bifocal glasses. He slept all afternoon. In the evening he cried a lot, complained of a mild headache, was quite restless, and wanted someone constantly near him. He was seen by a local physician in the evening and at that time he was able to perform finger-to-nose tests, and so forth, without any difficulty. Upon the advice of the physician he was sent to bed without specific treatment. About 11 P.M. he fell out of bed and did not seem to recognize his parents. He was quite restless for about one and one-half hours, after which he became comatose and displayed urinary incontinence. Upon the advice of a member of our attending staff, he was admitted to the hospital the following morning.

Physical examination on admission revealed a well-developed, well-nourished, white boy who was lying quietly in bed in coma. His temperature was normal. His pulse was full, regular, and 80 per minute. He was breathing quietly and regularly, approximately 22 times per minute. There was no evidence of Cheyne-Stokes breathing. Hyperpnea was not present. There was no acetone odor or other abnormal odor upon his breath. His blood pressure was 100/65. Examination of the head failed to reveal any evidence of injury. There was no rash or evidence of petechiae. The pupils were small, regular, and equal. Fundoscopic examination revealed some fuzziness of the right disc. No hemorrhage or retinal exudate was observed. The remainder of the physical examination was essentially negative except for the neurologic examination, which revealed a comatose child who responded only mildly to strong stimuli. All reflexes, deep and superficial, were absent. The corneal reflex was present bilaterally. Macewan's sign was negative. The Babinski was believed questionably positive. Kernig and Brudzinski signs were negative. There was no nuchal rigidity. The admitting impression was medulloblastoma of the cerebellum with hemorrhage into the tumor.

A complete blood count was normal. X-rays of the skull revealed normal skull table, sutures, and sella turcica. No abnormal shadows were seen. A lumbar puncture was performed. The fluid was crystal clear and was under mildly increased pressure. Unfortunately, the quantity obtained was insufficient for any analysis of the protein and chloride content; however, the sugar was 53 mg. per cent. The Pandy was negative. There were two cells per cubic millimeter and the culture of the spinal fluid was negative.

Dr. Douglas Buchanan saw this child about 1 P.M. At this time the child had aroused somewhat from his coma. He peered from half-closed eyes and answered questions in a sluggish manner. Dr. Buchanan confirmed the remainder of our neurologic examination except that he believed the optic discs were normal and that the blurring of the right disc was due to moderate astigmatism. He did not believe that the Babinski response was extensor. The deep and superficial reflexes were now present. The only additional significant findings that were observed was the absence of upward movement of both eyes upon voluntary effort and upon Bell's maneuver. In addition, there seemed to be a limitation of outward movement in both eyes. At that time x-rays of the skull had not been taken and the lumbar puncture had not been performed. On the basis of history and physical examination only, Dr. Buchanan felt that the most likely diagnosis was rupture of a congenital aneurysm of the circle of Willis.

During the course of the next four hours the child's condition changed astoundingly. At 5 P.M. he was neither comatose nor stuporous. He responded intelligently and promptly to all questions. There was no evidence of ataxia and the previously observed eye findings were now absent. He seemed somewhat euphoric but his parents observed that this was his normal state.

In summary, this child who was comatose at 9 A.M. had gone through various stages of recovery until at 5 P.M. he appeared entirely normal. He was again seen at this time by Dr. Buchanan, and after viewing the x-rays and seeing the results of the spinal tap, he stated that his earlier diagnosis was incorrect and that diagnosis of the condition would have to be deferred for the time being. He did not feel that the child had a neoplasm. The following morning the child was entirely normal. He had spent a restful night and had eaten a good breakfast. In the afternoon the mother came to the hospital and stated that she had found an empty capsule while cleaning the bathroom at home. She stated that there were in the medicine chest similar capsules which had been prescribed for her some fifteen years ago. Each of these capsules was found to contain three grains of Sodium Amytal. Upon interrogation the patient admitted that he took one capsule on Monday morning, two days before admission, and another capsule on Tuesday night, twelve hours before admission. As soon as these facts were obtained a urine specimen was collected and analyzed for barbiturates. The results of the analysis were negative; however, the fact must be remembered that this urine specimen was necessarily collected forty hours after ingestion of the second capsule.

We feel that this case represents an acute barbiturate poisoning manifested by staggering gait, coma, and neurologic findings which suggested a diagnosis of intracranial pathology.

Progress Note.—Since presentation of this case, this child has been home and has gone to school for one month. During this time he has complained of no headaches and has had no recurrence of symptoms similar to those described above.

DR. BIGLER.—What is Bell's Maneuver?

DR. BUCHANAN.—This is a test of considerable value in children and semi-comatose individuals to demonstrate the presence of normal conjugate deviation of the eyes, a reflex which is integrated in the mesencephalon between the superior colliculi. The upper eyelids are gently but firmly held open. The more the patient struggles to close his eyes the more clearly he will demonstrate the presence or absence of conjugate deviation. In the former case, the eyes roll upward.

DR. GIBSON.—What methods are recommended for treating barbiturate poisoning?

DR. BUCHANAN.—In children the ingestion of barbiturates is invariably accidental rather than intentional and, consequently, the total dose is usually less than in the adult attempting suicide. For this reason usually only expectant therapy is needed in children. Almost all cases involving children respond very well in six to twelve hours with nothing more than 5 per cent glucose in distilled water by slow intravenous drip. One milligram of picrotoxin as a single intramuscular injection may rarely be necessary.

DR. GIBSON.—Are there ever any residual changes in barbiturate poisoning?

DR. BUCHANAN.—Clinically, there are none. If the poisoning is fatal, there may be toxic, degenerative changes in the neurones of the cortex.

Case 4. Methemoglobinemia

DR. LEININGER.—Chief complaint: blueness.

We are presenting the case of a 15-day-old female infant who was admitted to this hospital on the tenth day of life. The past history revealed a normal pregnancy and uneventful labor and delivery, following which resuscitation of the infant was immediate. There are no other children in the family. The father and mother are both living and in good health. There is no history of familial diseases. The mother states that she saw the child shortly after birth and that the child appeared to be quite normal. The baby was given the first breast feeding on the third day and nursed for three days at four-hour intervals. Following almost every feeding the mother noted that the child regurgitated or vomited projectilely either part or all of the recently ingested food. On the sixth day the attending doctor took the baby off the breast and started a thickened feeding of Farina, evaporated milk, and water. At this time small doses of phenobarbital were given a short time before each feeding. Apparently the infant responded to this regime for she was sent home on the eighth day. The mother was instructed to continue with the thickened feedings and was given a prescription of "phenobarbital, belladonna, and a white chalky mixture." At the time of discharge from the hospital the infant had a normal pink color to the skin.

The parents followed instructions implicitly, giving the infant one-half teaspoonful of the medicine a few minutes before each feeding at four-hour intervals. Apparently the infant had no vomiting at home. The only effect that the parents observed following administration of the medicine was that the child would drop off promptly to sleep following the feedings. Shortly after

the 10 P.M. feeding, and following the fifth dose of the prescribed medicine, the parents observed the child's skin appeared dusky in color. The child did not vomit and did not appear particularly sick. The following morning the parents noted that the skin color was now quite dark, sufficiently so that they were greatly alarmed and brought the child to the hospital.

Physical examination at the time of admission revealed a well-developed, well-nourished, well-hydrated, white female infant 10 days old. She was quite active and was crying loud and vigorously. A very peculiar type of cyanosis of the skin was observed. It was not the typical bluish purple cyanosis of a child suffering from congenital heart disease nor the cyanosis of an infant suffering from atelectasis of the lungs, but rather a dirty, grayish-black tinge to the skin over the whole body but more pronounced around the lips, hands, and fingers. Complete physical examination was otherwise negative. The heart was normal in size, contour, and position, and no murmurs were heard. The lungs were clear to auscultation and percussion. The abdomen was neither distended nor scaphoid. The liver and spleen were not enlarged. The kidneys were not palpable. The stump of the umbilical cord was healing well. The anterior fontanel was not bulging. There were no neurologic findings suggestive of meningitis. The admitting diagnosis was methemoglobinemia, cause undetermined.

A complete blood count was normal. Urinalysis was reported negative. A blood specimen was drawn for examination and found to be almost chocolate brown in color. Quantitative analysis of the blood revealed 2.5 Gm. of methemoglobin and a spectographic study confirmed the presence of methemoglobin.

The pharmacist who had filled the prescription was called and we were informed that the prescription consisted of a tincture of belladonna 5 c.c.; phenobarbital 0.5 Gm., chalky mixture q. s. ad 120 c.c. Because of the normal dosage of phenobarbital and tincture of belladonna which was prescribed in this preparation, we were inclined to rule out the possibility of its having any bearing on the patient's present condition. Upon further interrogating the pharmacist, we learned that the chalky mixture which had been used was a preparation which had been compounded some two or three years ago. For this reason, he was unable to tell us precisely the contents of this mixture. Fortunately, the mother had sufficient foresight to bring the medicine with her to the hospital. We submitted it to the laboratory for analysis, especially requesting examination for bismuth subnitrate and nitrites. Qualitative analysis by means of the HCl-1₂-starch test was strongly positive for nitrites.

Before all of the above laboratory data were available, however, we had proceeded on the assumption that this represented a case of methemoglobinemia. A sterile aqueous solution of 1 per cent methylene blue was prepared and 0.5 c.c. was injected intravenously. Following this procedure, the child was observed for change in skin color. Fifteen minutes following injection of methylene blue there was a questionable improvement in the cyanosis. Twenty minutes after injection there was a definite improvement, but the child was

still quite cyanotic. At the end of a forty-five minute period, the child's skin had returned to the rosy pink color of the newborn infant, except for a slight dusky tinge of the toes, fingers, and lips. Clinically, therefore, we believe that the diagnosis of methemoglobinemia was established before we had obtained substantiating laboratory data.

The following day the child's color had returned entirely to normal and the only problem which remained was an inconstant and mild regurgitation of feedings. Occasionally, there was projectile emesis. However, the child responded well to the usual atropine and phenobarbital therapy and is at the present time retaining all feedings and gaining weight. She is now on a regular evaporated milk formula. The atropine has been discontinued and the elixir of phenobarbital has been reduced to one-half teaspoonful twice a day.

DISCUSSION

The problem of methemoglobinemia arises not infrequently in a pediatric hospital. Fortunately it does not occur as frequently as in the past, probably due primarily to the discontinuance of two therapeutic nitrates in diarrhea mixtures, however, bismuth subcarbonate has supplanted the former drug in view of the fact that nitrates have been demonstrated to be reduced to nitrites in the intestinal tract by the action of the normal bacterial flora; second, the appearance and use of sulfanilamide in the treatment of acute infections was frequently accompanied by some degree of cyanosis attributable to the formation of methemoglobin in the blood. The other common drugs which are known to cause methemoglobinemia are the chlorates and the nitrobenzene compounds, especially the aniline dyes. The last case of methemoglobinemia observed in this hospital occurred in an infant following a very brief contact with aniline dyes used in an identification marker in the diapers of a diaper service company.

The amount of methemoglobin which must be present in the blood stream to cause cyanosis is stated usually to be 3 Gm. per cent. However, this will vary in individual cases, as demonstrated by this infant who had a distinct cyanosis with only 2.5 Gm. per cent methemoglobin. The action of methylene blue in regard to methemoglobinemia is very interesting. For some time now methylene blue has been recognized as an invaluable drug in the treatment of cyanide poisoning. In this condition, the injection of large doses of methylene blue is accomplished in order to create a methemoglobinemia, whereupon the cyanide ion forms a loose bond with the methemoglobin and is rendered inert, following which the injection of potassium thiosulphate removes the cyanide ion as potassium thiocyanide. In the treatment, therefore, of cyanide poisoning, a methemoglobinemia is produced by large doses of methylene blue. On the other hand, many investigators have demonstrated the acceleration of conversion of methemoglobin back to hemoglobin following the injection of small doses of methylene blue. The usual dose of methylene blue recommended in the treatment of methemoglobinemia is 1.5 mg. per kilogram of body weight. This was the dosage used in the treatment of the patient discussed above.

DR. BIGLER.—Would you again list your causes of methemoglobinemia?

DR. LEININGER.—Sulfanilamide, cyanides, nitrates, nitrites, aniline, chlorates, and nitrobenzenes are the most common causes of methemoglobinemia. Of interest and worth noting are the occasional reports in the literature of methemoglobinemia occurring in infants whose milk formulas have been made with well water containing a high concentration of nitrates. In most of these instances cyanosis was not observed in adults drinking the same well water.

DR. GIBSON.—Is it necessary for any treatment other than altering the methemoglobin?

DR. LEININGER.—No. I think we should mention that prior to the use of methylene blue, transfusions of whole blood were used fairly effectively in treating methemoglobinemia. Oral administration of ascorbic acid also has been used, but results have been equivocal. The rationale of using ascorbic acid is based upon the fact that in vitro studies have shown that glucose, ascorbic acid, and niacin all have the property of transforming methemoglobin into oxyhemoglobin.

DR. GIBSON.—Is there any possibility of recurrence after treating a case of methemoglobinemia?

DR. LEININGER.—Not if the original cause is removed. Nitrates and nitrites, which constitute one of the major causes of methemoglobinemia, are absorbed as nitrites into the blood stream. Normally about 60 to 70 per cent of the absorbed nitrite disappears in the body, probably to be converted into ammonia. The remainder is excreted in the urine as nitrates and nitrites.

Psychologic Aspects of Pediatrics

THE BLIND CHILD

RUTH MORRIS BAKWIN, M.D.
NEW YORK, N. Y.

INDIVIDUALS with vision of less than 20/200 after correction are usually considered blind from the point of view of education. Those with vision of 20/70 to 20/200 in the better eye after correction are called partially sighted. A marked limitation of the field of vision will cause a severe enough handicap to classify the child as blind or partially sighted.

Incidence.—Estimates of the number of blind and partially sighted in the United States vary widely owing to the different definitions which are used and the unreliability of the methods of determining the extent of visual handicap. The estimate given by the White House Conference on Child Health and Protection in 1931¹ for school age children was 15,000 blind (about 0.5 per 1000) and 50,000 partially sighted (over 1.5 per 1000 school population) in this country. This is now regarded as too high. In 1948 in the United States almost 7,000 children were in schools and classes for the blind.

Etiology.—A report prepared by the committee on Statistics of the Blind in 1947² gave the principal causes of blindness in school children in the United States as follows:

Infectious diseases	19.8 per cent
Trauma	6.6 per cent
Poisoning	0.2 per cent
Neoplasms	3.7 per cent
General diseases	1.4 per cent
Prenatal origin	58.1 per cent
Etiology not specified	10.3 per cent

Conditions of prenatal origin include congenital cataract, retinitis pigmentosa, atrophy of the optic nerve, and glaucoma.

Blindness resulting from infectious diseases (gonorrhea, meningitis, measles, etc.) has been decreasing. Blindness from accident and injury is to some degree controllable, and measures are being undertaken through accident prevention campaigns to eliminate this factor. Consequently there is a relative increase in the percentage incidence of blindness of prenatal origin. In the future retrobulbar fibroplasia³ may become a prominent cause of visual impairment.

MENTAL FUNCTIONING

Intelligence.—Special tests, both individual and group, are available for measuring intelligence in the blind.⁴ They may be entirely oral, they may be

¹ From The Children's Medical Service of Bellevue Hospital, the Department of Pediatrics, New York University and the New York Infirmary.

dependent upon touch, or they may be given in Braille if the child is familiar with this method of reading. The reliability of the more recent tests is good.

The average intelligence quotient (I.Q.) of the blind is slightly below that of the seeing when tested on a scale prepared especially for the blind. When only those tests are used which can be given in exactly the same way to both groups, the average for the blind is about 10 points below that for the seeing.⁵ The percentage of high I.Q.'s, i.e., I.Q. over 120, is somewhat less than in seeing children. The greatest discrepancy is in the relatively large number of low I.Q.'s. Feeble-mindedness is much more common in the blind and borderline categories are larger.⁶

	BLIND (PER CENT)	SEEING (PER CENT)
Genius	0.3	0.5
Very Superior	1	2
Superior	5	9
Average	69	76
Dull	12.5	8
Borderline	7	2
Feeble-minded	5	0.3

One reason for this may be found in the conditions which cause blindness. Meningitis and encephalitis, for example, may lead to both loss of vision and mental impairment and the same is true for hydrocephalus and intracranial injury at birth. Whether this factor alone accounts for the frequency of low I.Q.'s among the blind as compared with the seeing is not known. The age at which vision is lost does not seem to affect the intelligence.⁷

Learning Ability.—No difference in learning ability was found when blind and seeing children of equal intelligence were tested.⁸

Memory.—The blind do not differ significantly from the seeing in the ability to memorize except that they are superior in special test situations where the material used is of a type with which they have had considerable practice such as reciting prose passages.

School Performance.—Blind children begin school, in general, somewhat late and they are therefore older than seeing children in the same grade. The schools for the blind in the United States have about the same standards as the public schools, but it takes blind children longer to cover the same amount of work and they therefore show educational retardation when compared with age norms for the seeing. The ones who start school at a younger age seem to do somewhat better than those who enter later.

Reading.—The use by the blind of special raised characters for reading was introduced in 1829 by Louis Braille who was himself sightless. Only about one out of five blind individuals now read Braille. Most are too old or find it too difficult to learn. The blind child of normal intelligence can be taught to read Braille at the end of the first year of study about as well as the seeing child reads print, but more slowly. His reading ability increases from grade to grade although his progress is in general slower than that of the seeing child. On the average the blind read only a third to a fourth as rapidly as the seeing. The rate in seventh grade is about 60 to 70 words per

minute as compared with 200 to 210 words per minute for seeing children. Given enough time the blind read at grade level but below age level. Standard English Braille, grade two, a system which makes use of contractions, is taught to the older children. This adds another difficulty which the seeing child does not encounter and explains, in part, his age retardation in school. Most tests have shown that Braille reading with both hands is fastest. According to German reports reading is faster with the left than with the right hand in one-handed reading⁹ but this has not been found consistently in America. As with seeing children there are poor, average, and good readers.

"Talking books,"¹⁰ first conceived by Thomas Edison, were introduced in the 1930's. They are long-playing (15 to 16 minutes) phonograph discs on which most of what is rewarding in classic and contemporary literature is recorded. The books are read by men and women experienced in stage and radio work. Many plays have been recorded with complete sets of actors reading the parts, and recordings for children have been "illustrated" with sound effects. The discs may be obtained on loan without cost from the Library of Congress or they may be purchased from the American Foundation for the Blind. Talking books for school age children are available through the American Printing House for the Blind in Louisville, Kentucky. The portable reading machines may be obtained from a local agency in each state or they may be bought. Thus far a considerable amount of material has been recorded. This method is more rapid than Braille reading.

Electronic and various other devices are being developed with which it is hoped that the blind may be able to read printed material.

Writing in Braille is done by punching small dots in paper with a stylus. In order to be read, the paper is turned over so that the raised dots may be felt and the writing therefore must be from right to left. Machines called "Braille writers" are available and blind children may also learn to use ordinary typewriters.

Speech.—Blind children begin to talk later than the seeing since they must learn to imitate movements of speech which they have never seen. Moreover, they may have been living in the unstimulating environment of an institution, or the parents may be uninformed as to the special help which blind children need in order to learn to talk. Speech defects are quite common. Once they learn to speak they indulge in it more than seeing children. They ask a great many questions, principally about the objects in their environment. Proper names are used frequently.

Clay modeling gives interesting insight into the conceptions which the blind have about the world. They frequently model things to eat and they make human beings with heads much too large and too full of detail.

In spite of the difficulties in learning, the blind of superior intelligence may attain positions of eminence in the world. A notable example is Helen Keller who lost her sight and hearing through illness at 19 months of age. Despite her handicaps she graduated "cum laude" from Radcliff at 28 years of age. She wrote several books in which her optimistic outlook on life and

the excellent literary style show the efficiency of modern education for the blind. Maria Theresa von Paradis, born in the eighteenth century, was blind and was educated by a blind teacher. She became a prominent musician and toured Europe as a concert artist. John Milton became blind when 43 years old. After this he wrote his greatest work "Paradise Lost," as well as several other poems.

Special Abilities.—The blind pay attention to slight changes in pitch and in pressure, thus recognizing movement, objects in the way, etc. This has been called "the sense of obstacles" and is not fully understood at present. No evidence has been produced to support the theory of a special sensory compensation, that is, the increased sensitivity to sound, touch, taste, or smell, so often attributed to the blind. The blind person is endowed neither with superior memory nor with special ability to recognize people by the voice alone nor to interpret their moods, etc., but he can become more skillful in all these activities by practice. Owing to his visual handicap he must rely more on his other senses and so he cultivates them.

PERSONALITY

Certain personality attributes are commonly found in blind children. They are self-centered and less competent socially than seeing children of the same age. The reason for this is to be found in their difficulty in getting about and meeting people. The home environment is necessarily arranged for their convenience and as a result they may be overindulged and relieved of responsibility. One personality study revealed that they were extremely suggestible, felt inferior, had many fear reactions, but accepted their handicap without bitterness. In another survey, of 105 blind children tested, 101 said they would rather be blind than deaf. Other personality tests corroborating these findings showed that, in general, blind children were unduly sensitive, showed less initiative, and were easily discouraged but were not rigid or remarkably withdrawn. As a group they were more "maladjusted" than the seeing. There seemed to be no more tendency for the blind to show introversion or extroversion than the seeing.

Sommers¹¹ concluded from her study of the adolescent blind that personal and social adjustment of the blind cannot be adequately measured by tests at present available and that the effect of blindness can be evaluated only in relation to the total social environment of the individual. Emotional maladjustments result more frequently from the attitudes of the parents toward the child and his handicap than from the visual disability itself. The environment in which he lives will certainly influence the child's personality. The stultifying effect of residence in an institution is an important factor influencing the personality of many blind children. Custodial care, with little opportunity for education, is the only kind available in most communities for blind children of low I. Q.

The blind child needs help in developing a personality which will make it possible for him to associate normally with the seeing. Fortunately we are

more kind in our relations to the blind than the deaf. The blind child is obviously handicapped and helpless in getting about under most circumstances. We willingly help him. This in turn allows him to develop a more open personality.

EDUCATION

There are two types of schools for the blind. They may attend Braille classes in the same day schools as normal children and thus take part in regular classroom instruction. They thereby benefit from living at home and maintaining contacts with nonhandicapped individuals. The other type is the residential school. There are over sixty of these in the United States at present, most of which are free. An attempt is made to give the child the same educational opportunities and experiences as sighted children. The disadvantage of this type of school, aside from the fact that the child is away from home, is that he is segregated from seeing children and so lacks preparation for living in a sighted world. Efforts are now being made to teach as quickly as possible the special techniques and materials which are necessary, and then to return the blind children to regular day school. With some provision for Braille, talking books, or a reader, many children seem capable of making this adjustment at the end of grammar school.

At present residential schools for the blind provide education for about 90 per cent and Braille classes for the remaining 10 per cent of blind children attending school. In 1948 Braille classes were conducted in public schools in twenty-five cities in the United States. When educational facilities are available, most parents seem able to cope with the blind child in the home.

OCCUPATION

There has been some disagreement as to whether vocational training should be included in the high school course or given later. It has been suggested that if the education were less verbal and more objective it would be more efficient in preparing the blind for the future. In a follow-up study of 337 blind pupils from the Pennsylvania Institute, Sargent¹² found that over one-half (53.7 per cent) were self-supporting or better, and only 18.1 per cent were completely dependent. The occupations most frequently carried on by men were piano tuning and chair caning, and by women housework and chair caning with weaving and basketry next. Recent experiences have shown that many other jobs requiring manual dexterity and concentrated attention can be handled successfully by the blind.

CARE OF THE BLIND CHILD

Guidance.—The parents of the blind child have a difficult task. They must learn to accept their child and not be frightened or bewildered because of his defect. Special institutes and study groups have been set up in various parts of the United States to help them understand how to meet their problems. There are summer camps for blind children and their mothers in some states, and these have assisted materially in establishing techniques of training.¹³

Seeing children learn, in great part by imitation, the techniques of walking, talking, and feeding themselves, but the blind child is deprived of this advantage. The parents must understand that, with help in learning, the blind child will be able to undertake much that a seeing child can do but at a slightly later age. He must have freedom to move about, to manipulate objects, to play with nonhandicapped children, and to do everything for himself that he is capable of doing. He must have a chance to succeed, he must be praised and reassured, and at the same time he needs to be given responsibility within the limits of his developmental status and his handicap.¹⁴

The blind child needs more help in learning than the seeing child who is constantly stimulated through vision. The seeing child reaches for attractive objects, he crawls toward playthings, he runs to get a toy. A blind child lacks these stimuli and therefore objects must be brought to him. He learns through sounds, touch, manipulation. He needs playthings which provide varied experiences such as toys of different shapes, sizes, and textures, and toys that make different sounds. In presenting an object to the blind child, its name and something of its structure and use should be told to him. "This is a cup. It is white and hard and shiny. It is made of china. Plates are made of china also. This cup has milk in it but it can hold water or tea. It is to drink from." This simple explanation helps the child to recognize the object again. While the child is young it is best to name any object given to him, so that he will be prepared for its weight and size.

There should be sounds in the environment for these mean much to the blind child.¹⁵ The mother should speak when she enters the room and as she moves from place to place. The child can follow her movements by her voice. Music, musical blocks, and squeak toys are stimulating. For the small baby, toys may be tied to the crib in certain places so that he will know where to find them. He can easily reach wooden beads strung across his crib or a squeaky doll tied to the crib rail. When he gets the toy for himself, it is the first step toward independence.

Extra encouragement and help are needed in walking. Fear is a great deterrent. Creeping is rare in blind children. Walking must be encouraged by interesting sounds. At first the child must be led by the parent, then he can go a short distance from one person to another with only a guiding hand, later with only a guiding voice. A play-pen often helps as he can walk about it holding on. When the baby can walk alone, he must be allowed to investigate his environment. At first objects he would bump into or trip over should be removed, but presently he will know objects in a familiar room and avoid them. Deliberate easy walking should be encouraged rather than running about, since falls are likely to frighten the child badly. The child who walks slowly and pays attention will usually sense objects nearby. He should be taught not to stretch out his hand to protect himself since this is an unpleasant mannerism. Rather he should learn to touch objects with the arms at the side as he passes by, so as to become familiar with them.

The blind child of normal intelligence can learn to feed himself without too much difficulty. At first he should hold the spoon with the mother guiding his hand just as any other child. A little more patience is required. Food should be put on his plate in a certain way, meat at the upper right, potato lower right, etc., so that he will know what to expect. Training for self dressing, undressing, and washing may be started at about the same age as for the seeing child. A little longer is needed in learning but with the proper training the blind child will not be greatly retarded.

The blind child should not be confined to the home. He should ride in buses and trains, he should visit friends, he should go to the zoo and listen to the animals. If his parents will describe their appearance at the same time, telling size, shape, and color, he will know much that the seeing child knows, and he will be able to talk more understandingly with other children. The isolation which is inflicted upon so many blind children is really more of a handicap than the lack of vision. Social intercourse is the best way to make the blind child feel at home with other children.

Some blind children retreat into an imaginary world and avoid facing realities. This is much less likely if life is made interesting. Social contacts are the most important part of helping the child to live realistically. A healthy attitude on the part of the parents and siblings will help relatives and friends to accept the blind child in the same way.

Neatness and orderliness are essential to the blind person. It is obvious that he will get about much better if he knows where every piece of furniture is and that he will find his clothes more easily if they are always in their proper places. Also, as the blind person cannot see himself, he must be especially careful about his clothes and his person. The blind child should be taught tidiness at an early age and this should be emphasized until he himself can appreciate the advantages. The parents and siblings, too, must learn to keep the house in order so that the blind child will feel secure in moving about.

In teaching the blind child it is necessary that verbal instructions be given clearly and concisely. He may miss some detail of the total situation, which is readily apparent to seeing people from a gesture or a facial expression. Consequently, the request is not clear to him and he then appears to be stupid, willful, or disobedient when he is really confused.¹⁴

Preschool teaching is very similar to teaching the seeing child of the same age, except that more conscious effort is required. Children are not accepted into most kindergarten classes of the schools for the blind before 5 years of age. Some blind children and most partially sighted children are accepted in public kindergartens and go to special classes or schools only after 6 years of age. Typewriting gives the child an easy way of written communication and of expressing his thoughts, but does not help him in reading. In general, when the child is ready to read, usually at about 6 years of age, he must be taught Braille. A matter-of-fact attitude about the necessity of his reading with his hands whereas another child reads with his eyes is usually beneficial in helping the child to accept this technique. He needs encouragement in reading and in

undertaking schoolwork, but if of normal intelligence, he will succeed. If the parent will learn Braille also, he will be able to write to his child and read the child's letters without the help of a third person. This gives the child assurance that his parents are interested in helping him in every way and brings the parents closer to the child.

Blind children should be taught as much as possible by actual experience. Models can be used when objects as such cannot be observed. Verbal description alone should be avoided whenever actual experience can be supplied. The sense of touch is the essential medium for the blind child's acquisition of the basic knowledge of objects.

Standards are set up in most states by the Board of Education for the education of the blind and partially sighted.

Most blind children must be taught techniques of behavior which come more naturally to the seeing child who learns through actual observation. They should walk with the head erect and face the person to whom they are speaking. Certain habitual movements are unpleasant and should be discouraged. One of these, repeated rubbing of the eyes, may begin in infancy and persist into adult life. Shaking and rolling the body, poking at eyes and ears, shaking the hands when excited and, if there is some vision, fanning the fingers in front of the eyes are other undesirable mannerisms known as "blindisms." As soon as these habits appear the parent or teacher should attempt to stop them by gentle reminders, and particularly by keeping the child occupied constructively, as these mannerisms are less frequent when he has something interesting to do. They are by no means an indication of inferior mentality and are given up as the child grows older.

As the blind child matures he, like the seeing child, shows increasing interest in music and literature. Parents can assist their children to enjoy these by making use of the radio, phonograph, and concert hall. Blind children can be taught to play various musical instruments. A considerable amount of music is published in Braille and many Braille books are available for children.

Parents should familiarize themselves with modern concepts of the care and education of the blind.¹⁶ They should not neglect, however, the literature on the normal child since the principles underlying the care of the seeing child relate as well to the blind.

Information regarding all aspects of the care of the blind can be obtained from:

The American Foundation for the Blind, Inc., 15 West 16th Street, New York 11, N. Y.

New York Association for the Blind, 111 East 59th Street, New York 22, N. Y.

Books which may be recommended to parents are:

Guide for Parents of a Preschool Blind Child, Commission for the Blind of the New York State Department of Social Welfare, New York, 1945.

Speer, E. L.: *A Manual for Parents of Pre-School Blind Children*, New York Association for the Blind, New York.

Totman, H. E.: *What Shall We Do With Our Blind Babies?* American Foundation for the Blind, New York, 1938.

Tests which can be used for testing the blind:

Individual Tests.—

Interim Hayes-Binet Tests for the Blind 1942, based on the 1937 L-M Series of Terman and Merrill, *Outlook for the Blind* 37: 37, 1943.

Wechsler-Bellevue Adolescent Scale, Verbal and Vocabulary Tests, Psychological Corporation, 522 Fifth Avenue, New York, N. Y.

Personality Tests.—

Adaptation of the Vineland Social Maturity Scale for use with blind children by Maxfield, K. E., and Fjeld, H. A.: *Child Development* 13: 1, 1942.

REFERENCES

1. White House Conference on Child Health and Protection, Special Education Section IV, Committee B.: *The Handicapped*, New York, 1931, Century Co., p. 292.
2. Kerby, C. E.: What Causes Blindness in Children? Eye Conditions Among Pupils in Schools for the Blind in the United States 1945-46, *Sight-Saving Review* 18: 21, 1948.
3. Terry, T. L.: Ocular Maldevelopment in Extremely Premature Infants, *J. A. M. A.* 128: 582, 1945.
4. Hayes, S. P.: Mental Measurements of the Blind, in *What of the Blind?* II New York, 1941, American Foundation for the Blind.
5. Pintner, R., Eisenson, J., and Stanton, M.: *The Psychology of the Physically Handicapped*, New York, 1941, F. S. Crofts & Co., Chaps. VII and XII.
6. Hayes, S. P.: Contributions to a Psychology of Blindness, New York, 1941, American Foundation for the Blind.
7. Hayes, S. P.: Factors Influencing the School Success of the Blind, *Teachers Forum (Blind)* 6: 91, 1934.
8. Koch, H. L., and Ufkess, J.: A Comparative Study of Stylus Maze Learning by Blind and Seeing Subjects, *J. Exper. Psychol.* 9: 118, 1926.
9. Smith, J. M.: Which Hand Is the Eye of the Blind? *Genet. Psychol. Monographs* 5: 213, 1929.
10. Lowenfeld, B.: Braille and Talking Book Reading, A Comparative Study, New York, 1945, American Foundation for the Blind.
11. Sommers, V. S.: The Influence of Parental Attitudes and Social Environment on the Personality Development of the Adolescent Blind, New York, 1944, American Foundation for the Blind.
12. Sargent, R. F.: *What Can the Blind Do?* Overbrook, Philadelphia, 1924, Pennsylvania Institution for Instruction of the Blind.
13. Bull, J.: If Your Baby Is Blind, *The Crippled Child*, Dec., 1947.
14. Guide for Parents of a Preschool Blind Child, Commission for the Blind of the New York State Department of Social Welfare, New York, 1945.
15. Totman, H. E.: What Shall We Do With Our Blind Babies? in *What of the Blind?* New York, 1938, American Foundation for the Blind.
16. Lende, H.: Books About the Blind, a Bibliographical Guide to Literature Relating to the Blind, New York, 1940, American Foundation for the Blind.

Comments on Current Literature

THE USE OF GLUTAMIC ACID IN THE TREATMENT OF MONGOLISM

THE use of *l*(+)-glutamic acid in the treatment of patients with defective mental function has been based on experimental studies which indicate that this amino acid is peculiarly important in the metabolism of nerve tissue. According to Weil-Malherbe¹ *l*(+)-glutamic acid is the only amino acid known to be metabolized by slices of brain tissue. By *in vitro* experiments²⁻⁴ it has been shown that glutamic acid acts as a catalyst in complex enzyme chain reactions which are necessary for the production of electrical nerve impulses. Experimental results with white rats indicated that maze learning was significantly enhanced by the addition of glutamic acid to the diet.

Encouraged by results obtained in the treatment of mentally retarded children (*American Journal of Psychiatry*),⁵ Zimmerman, Burgemeister, and Putnam undertook a special clinical study of the effect of glutamic acid on the mental function of patients with mongolism, and in the March, 1949, issue of the *Archives of Neurology and Psychiatry*⁶ they publish a preliminary report. Seven typical mongoloid patients, three girls and four boys, ranging in age at the time of the initial test, from 3 years, 6 months, to 14 years, 1 month; were included in the clinical study. These authors point out that the dosage for each patient must be worked out on an empirical basis determined by careful testing and clinical observation. The particular dose of glutamic acid which stimulates maximum mental function is the optimum for a given patient. In this study of seven patients, the range of daily dosage was as follows: 12 Gm., 18 Gm., 24 Gm., 24 Gm. and 48 Gm. Medication was given orally in three divided doses. No side effects were observed except occasional gastric distress. Each patient received glutamic acid for a period of six months.

Prior to glutamic acid therapy, each child was rated by means of the Stanford-Binet intelligence test and the Merrill-Palmer performance test. When the intelligence test was repeated at the end of the six months' period, all seven of the children with mongolism showed some rise in the intelligence quotient after glutamic acid therapy, the increments ranging from 1 to 20 points. The average mental age was raised from 3 years, 6 months, to 4 years, 2 months, a gain of eight months in the six months' treatment period. The authors state: "Our results suggest that, under the conditions of our experiment glutamic acid definitely facilitates mental functioning in our children with mongolism."

In contrast to the gains made on verbal material, the group with mongolism did not show striking improvement on the nonlanguage, or performance, type of test. Approximately the same increment was maintained on motor tests during treatment as that previously recorded in the absence of treatment. Failure to improve the performance on motor tests might be explained on the basis of pathologic changes in the spinal cord as described by Benda,⁷ who showed that the spinal cord of patients with mongolism has a characteristic picture ranging from hypoplasia to true fetalism, with arrested development and pathologic differentiation. This type of pathologic involvement of the cord would explain amply the impaired coordination of muscular activity. Zimmerman, Burgemeister, and Putnam point out that learning depends on

the transmission of sensations from the environment by nerve impulses which are integrated into a state of conscious awareness, and intelligence appears to depend basically upon the degree of conscious awareness. Glutamic acid, by aiding the production of electrical impulses, would increase the degree of conscious awareness, thus facilitating the learning process.

This report, although preliminary in nature, offers valid evidence in favor of the use of glutamic acid in the treatment of patients with mongolism. Since mongolism is one of the more serious and more common forms of mental deficiency, and since there is so little to offer therapeutically, any encouraging note is welcome.

RUSSELL J. BLATTNER.

REFERENCES

1. Weil-Malherbe, H.: Studies on Brain Metabolism: Mechanism of Glutamic Acid in Brain, *Biochem. J.* 30: 665, 1936.
2. Nachmansohn, D., Cox, R. T., Coates, C. W., and Machado, A. L.: Action Potential and Enzyme Activity in the Electric Organ of *Electrophorus electricus*: II. Phosphocreatine as Energy Source of the Action Potential, *J. Neurophysiol.* 6: 383, 1943.
3. Nachmansohn, D., and Machado, A. L.: The Formation of Acetyl-choline: A New Enzyme, "Choline Acetylase," *J. Neurophysiol.* 6: 397, 1943.
4. Nachmansohn, D., John, H. M., and Waelsch, H.: Effect of Glutamic Acid on the Formation of Acetylcholine, *J. Biol. Chem.* 150: 485, 1943 (Letter to the Editors).
5. Zimmerman, F. T., Burgemeister, B. B., and Putnam, T. J.: The Ceiling Effect of Glutamic Acid Upon Intelligence in Children and in Adolescents, *Am. J. Psychiat.* 104: 593, 1948.
6. Zimmerman, F. T., Burgemeister, B. B., and Putnam, T. J.: Effect of Glutamic Acid on the Intelligence of Patients With Mongolism, *Arch. Neurol. & Psychiat.* 61: 275, 1949.
7. Benda, C.: *Mongolism and Cretinism*, New York, 1946, Grune & Stratton, Inc.

News and Notes

The following were certified by the American Board of Pediatrics at the examination held at Baltimore, Md., May 7, 8 and 9, 1949.

- Dr. Gunnard John Antell, 310 Coral Way, Coral Gables, Fla.
Dr. Robert Thomas Bandi, 901-4 Central Union Bldg., Wheeling, W. Va.
Dr. George H. Barmeyer, The Western Montana Clinic, Missoula, Mont.
Dr. Leo M. Bashinsky, 2028 Highland Ave., Birmingham 5, Ala.
Dr. Selma Buchbinder, 74 No. Village Ave., Rockville Center, N. Y.
Dr. Edgar L. Clayton, 3 Aldin Lane, Levittown, Hicksville, N. Y.
Dr. John Fielding Crigler, Jr., Harriet Lane Home, Baltimore 5, Md.
Dr. George F. Cunningham, 615 Third St., Brooklyn, N. Y.
Dr. Edward Davens, 2411 North Charles St., Baltimore 18, Md.
Dr. Matthew Debuskey, 2412 Eutaw Place, Baltimore, Md.
Dr. John Henry Dent, Tulane University of Louisiana, New Orleans, La.
Dr. Joseph Dolgin, 33 Central Ave., St. George, Staten Island, N. Y.
Dr. Richard Edward Dormont, Louisiana State University, New Orleans 13, La.
Dr. S. Chester Dunn, 227 W. Kleberg, Kingsville, Texas.
Dr. Anny Elston, 242 East 15th St., New York 3, N. Y.
Dr. Theodore S. Golden, 118 Union Ave., Framingham, Mass.
Dr. Seymour Gruber, 640 Eastern Parkway, Brooklyn 13, N. Y.
Dr. Harriet Griggs Guild, Johns Hopkins Hospital, Baltimore 5, Md.
Dr. Janet Baillie Hardy, Johns Hopkins Hospital, Baltimore 5, Md.
Dr. Paul Harold Hardy, Jr., Johns Hopkins Hospital, Baltimore 5, Md.
Dr. Horace L. Hodes, Sydenham Hospital, Baltimore, Md.
Dr. Laslo Kajdi, Johns Hopkins Hospital, Baltimore 5, Md.
Dr. Maurice J. Keller, 101 Federal St., Salem, Mass.
Dr. Marjorie B. Klugherz, 2100 Avenue J., Brooklyn 10, N. Y.
Dr. Bernard Laski, Hospital for Sick Children, 67 College St., Toronto, Canada.
Dr. Harold I. Lecks, 5701 Ogontz Ave., Philadelphia, Pa.
Dr. Elizabeth Sarah Linson, 214 North Potomac St., Hagerstown, Md.
Dr. James Neill Lysaught, Johns Hopkins Hospital, Baltimore 5, Md.
Dr. Milton Markowitz, Johns Hopkins Hospital, Baltimore, Md.
Dr. Lillian Francis McMackin, 71 Blue Hill Parkway, Milton, Mass.
Dr. Jack Metcalf, 300 Longwood Ave., Boston, Mass.
Dr. Thomas Edward Mosher, 525 East 68th St., New York 21, N. Y.
Dr. John Oliver Nestor, 2170 North Glebe Rd., Arlington, Va.
Dr. Thomas Lewis Rider, 959 Washington Ave., Albany, N. Y.
Dr. Martin Rothman, 91 Emerson St., Haverhill, Mass.
Dr. Justin Rubin, 5927 Pine St., Philadelphia 43, Pa.
Dr. Marie Esther Russell, 583 Haddon Ave., Collingswood, N. J.
Dr. Edward A. Sawan, 797½ N. Main St., Akron, Ohio.
Dr. Alexander J. Schaffer, 8 East Eager St., Baltimore 2, Md.
Dr. Francis F. Schwentker, Johns Hopkins Hospital, Baltimore 5, Md.
Dr. Francis F. Silver, 9400 Euclid Ave., Cleveland 6, Ohio.
Dr. George Roland Spence, 904 Ellsworth Dr., Silver Spring, Md.
Dr. Melchiah Spragins, 102 Alleghany Ave., Towson, Baltimore 4, Md.
Dr. Frank Ashbrook Stewart, 34 Bull St., Newport, R. I.
Dr. James B. Stewart, 12900 Euclid Ave., East Cleveland, Ohio.
Dr. Ethon L. Stone, 143 North Jackson St., Jackson, Mich.
Dr. Helen B. Tausig, Johns Hopkins Hospital, Baltimore 5, Md.
Dr. Grant Taylor, Duke Hospital, Durham, N. C.
Dr. William Joseph Temple, 1 Wallace Ave., Covington, Ky.
Dr. Elizabeth Peabody Trevett, 210 Prince George St., Annapolis, Md.
Dr. Maya Stromberg Unna, 23 W. Calendar Ave., La Grange, Ill.

At the annual meeting of the American Pediatric Society at Atlantic City, the following officers were elected for 1949-1950:

President: Dr. Philip C. Jeans, Iowa City.

Vice-President: Dr. Katharine Dodd, Cincinnati.

Secretary-Treasurer: Dr. Henry G. Poncher, Chicago.

The next annual meeting will be held at French Lick, Ind., the last week of April, 1950.

The National Foundation for Infantile Paralysis has announced short courses for physicians in the diagnosis and treatment of poliomyelitis patients as follows:

<i>Training Center</i>	<i>Scheduled Courses</i>	<i>For Detailed Information and for enrollment write to: William T. Green, M.D.</i>
Children's Hospital Boston, Mass.	June 13-17 Aug. 15-19	John A. Toomey, M.D. Department of Contagious Diseases
City Hospital Cleveland, Ohio	July 18-23 Aug. 8-13 Aug. 29-Sept. 3	Jessie Wright, M.D. Medical Director
D. T. Watson, School of Physical Therapy Lectsdale, Pa.	1 to 3 weeks, depending on need of each individual. Dates to be specially arranged. Emphasis on when to pre- scribe the respirator and when the rocking bed, with varia- tions to meet the needs of each patient.	
Georgia Warm Springs Foundation Warm Springs, Ga.	3 to 6 months, starting July 5, and October 3.	Robert L. Bennett, M.D. Director of Physical Medicine
Stanford University School of Medicine San Francisco, Calif.	3 days—probably the second week in July.	W. H. Northway, M.D. Assistant Dean
University of Colorado Medical Center Denver, Colo.	May 23-28 Nov. 14-19	Winona C. Campbell, M.D. Director of Poliomyelitis Teaching Program

The Seizure Division of the Children's Medical Center of Boston offers a fellowship of six months for work in epilepsy and electroencephalography. For information, write to William G. Lennox, M.D.

The following officers have been elected by The Society for Pediatric Research for 1949-1950:

President: Francis F. Schwentker

Vice-President: Harry H. Gordon

Secretary-Treasurer: Robert Ward

The meeting place for 1950—French Lick, Ind.

Book Reviews

Cardiac Catheterization in Congenital Heart Disease by André Cournand, Janet S. Baldwin, and Aaron Himmelstein. 41 East 57th Street, New York 22, N. Y., 1949, The Commonwealth Fund, 108 pages. Price \$4.00.

This book was written to explain the theoretical and practical considerations in cardiac catheterization as applied to congenital heart disease. The book is divided into two parts. Part 1 gives in detail in four chapters the equipment and techniques used for the catheterization procedure; complications are also listed. X-ray plates are shown to illustrate the position of the catheter tip in the various chambers of the heart and great vessels. Blood pressure tracings are shown to illustrate the findings in the various chambers of the heart. The different formulas needed for calculation of systemic and pulmonary blood flow are included.

Part 2 includes seventeen illustrative cases of various types of congenital heart disease. Each case has a brief summary of the history and physical examination together with the pertinent laboratory data. The results of cardiac catheterization are completely listed in a diagrammatic fashion, so that it is very easy to see the various malformations which the authors wish to show.

This should be an extremely useful book for anyone who is interested in cardiac catheterization. It should be particularly helpful to those who are in the process of setting up a laboratory for this type of investigation.

CARSON.

Aesculapius Comes to the Colonies. The Story of the Early Days of Medicine in the Thirteen Original Colonies. Maurice B. Gordon, M.D., Ventnor, N. J., 1949, Ventnor Publishers, Inc., 560 pages. Price \$10.00.

This is an exceedingly interesting account of medical men and medical practices in the colonial days of America. Each of the thirteen original colonies is considered in a separate chapter. The development is largely along the line of biographical sketches of the early physicians and the part each played in the early days of medicine in their locality. The book is thoroughly illustrated. It is well-written and the doctor will find it good casual reading for his spare moments and relaxation.

The Uses of Penicillin and Streptomycin. Chester S. Keefer, M.D., Lawrence, Kansas, 1949, University of Kansas Press, 72 pages. Price \$2.00.

Three Porter Lectures (Series 15) delivered at the University of Kansas School of Medicine by Dr. Keefer of Boston, an outstanding authority on the use of the antibiotics, compose this book. The first lecture is on Penicillin in Medical and Surgical Practice, the second on Streptomycin in the Treatment of Infections, and the third is entitled Antibacterial Agents From Microbes. In these lectures the author has presented the use of the two antibiotics in a direct and clear way. It is an authoritative presentation of their use and limitations which summarizes present-day knowledge.

The Compleat Pediatrician. W. C. Davison, M.D., ed. 6, Durham, N. C., 1949, Duke University Press. Price \$4.75.

Dr. Davison in the sixth edition of "The Compleat Pediatrician" has continued to keep it abreast of current medical knowledge. The reviewer checked it for a number of recent developments and found them all in the new text. It is one of the few books that has steadily improved with each new edition, and over the years has won a much deserved place among the books that are "musts" for the pediatrician. We can only repeat previous reviews in THE JOURNAL that it is "invaluable" and "a veritable mine of information." This opinion, expressed in the early reviews, has been definitely established.

Editor's Column

PEDIATRIC RESIDENCIES

THE annual report on hospital residencies of the Council on Medical Education and Hospitals of the A.M.A.* makes for thoughtful reading. The report shows that as of May 1, 1949, there were 211 hospitals approved for "residency training" in pediatrics with a total of 959 positions for residents and assistant residents available. Ten years ago there were only 105 approved hospitals with 330 positions. Thus in a decade the number of approved hospitals has been doubled and the number of positions increased threefold. Much of this has taken place since 1945, when the approved hospitals numbered 131 and the positions 504. This increase of 60 per cent in the number of hospitals and 90 per cent in the number of positions in the last five years resulted in large part from the demands created by the accelerated medical school teaching during the war and after the war by the large number of returning medical officers entitled to continue their education with government aid. If this number of positions continues to be filled in future years, which we doubt, it would mean about 450 young doctors entering pediatrics as a specialty each year and eligible for certification. This would more than double the present number of pediatricians in a decade when it has taken over three decades to train the present specialists.

We question very much if this will happen, but feel that many of the hospitals will be unable to fill these recently created "approved residencies" in the very near future. Already we have heard of a number seeking applicants. The younger physicians will undoubtedly seek residencies in the hospitals where the best training can be obtained, despite the high stipend now paid by some hospitals in comparison with the low stipend paid by many of the better medical centers for children.

It is interesting to note that at present 17,293 residencies are offered in twenty-six specialties in 1,187 hospitals approved for residency training. According to our calculation, if every medical graduate, after a year of internship, spent the next two years in residency training for a specialty, these graduates would fill about 12,000 of the 17,000 residencies offered. It does not take a prophet but only common sense to realize that the balloon of specialty training, which has been so rapidly inflated in the last few years, will soon undergo a partial collapse, to say the least.

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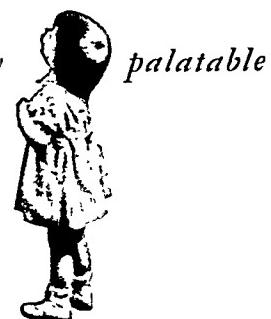
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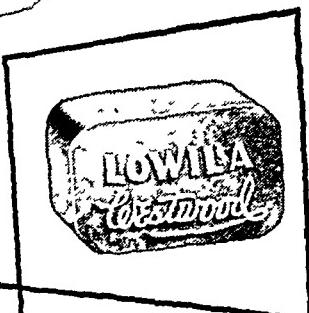
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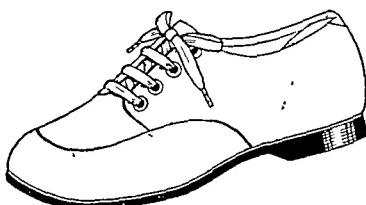
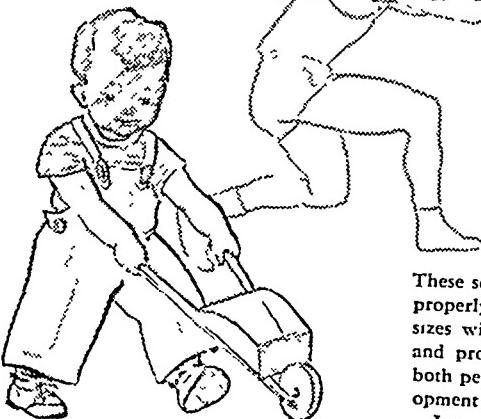
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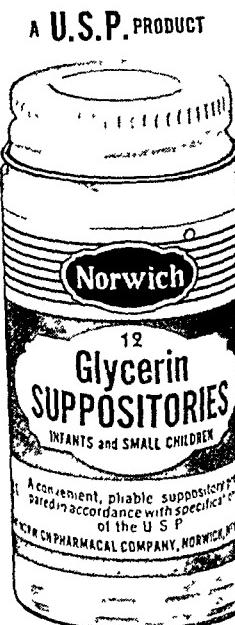
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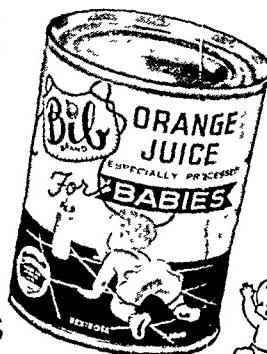
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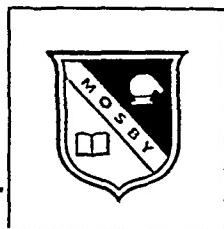
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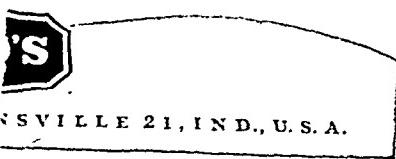
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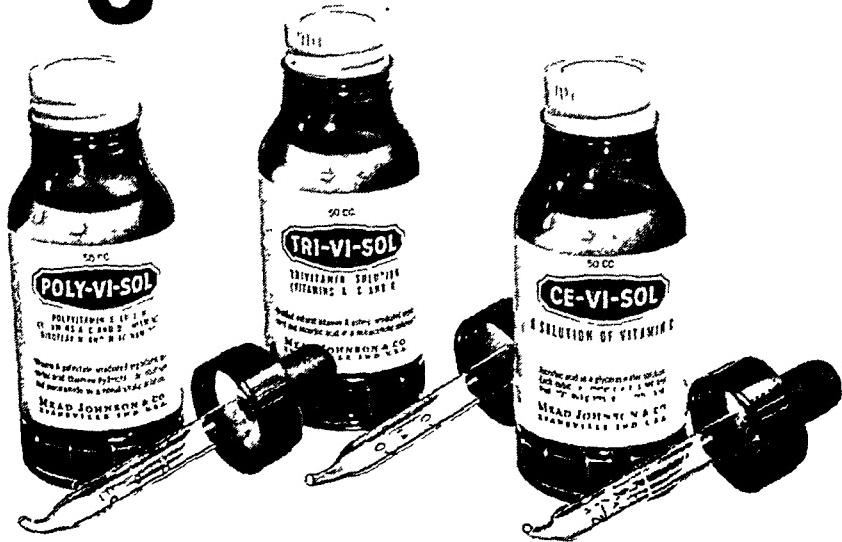
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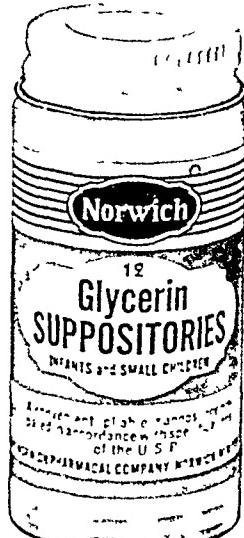
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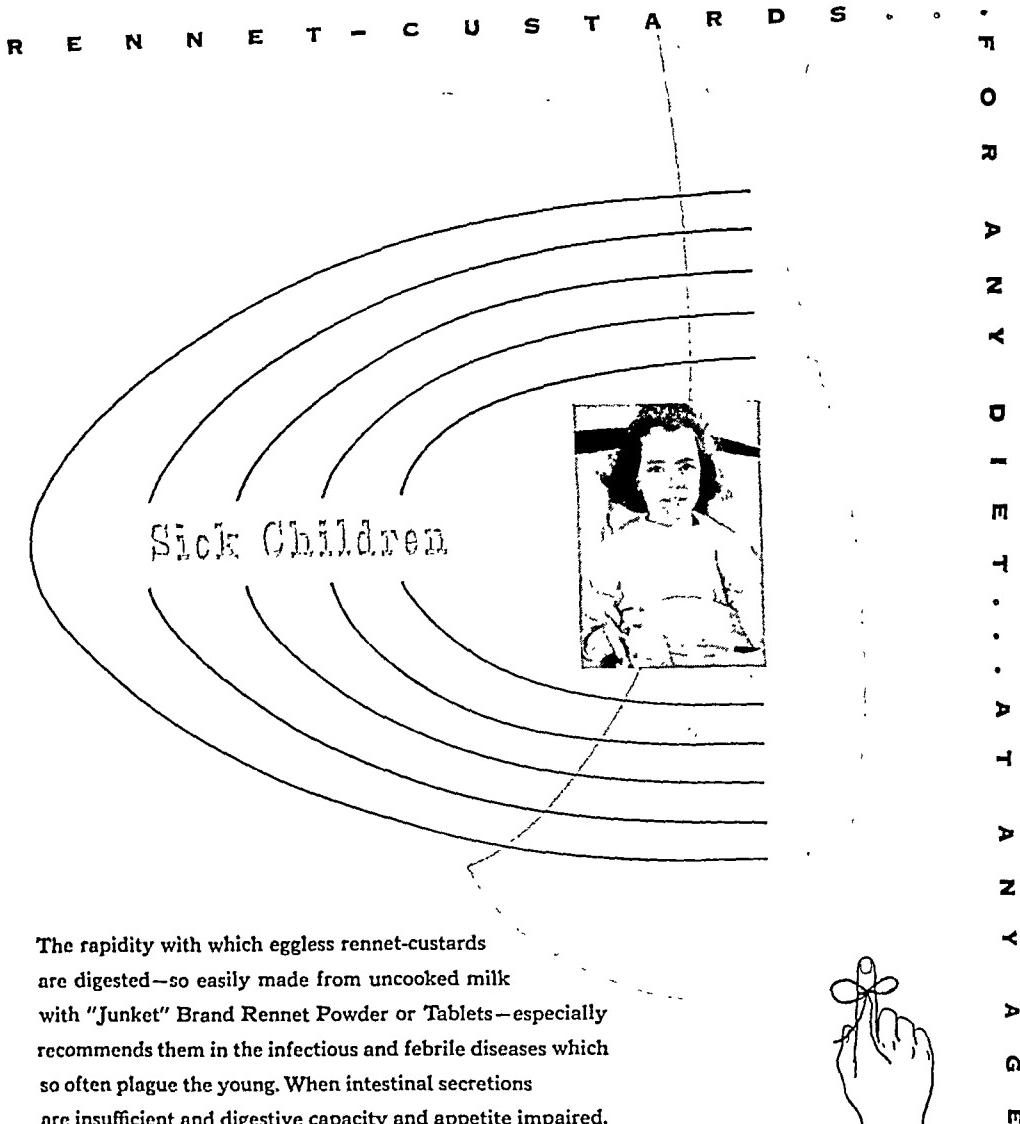
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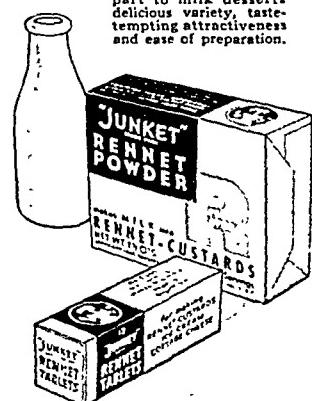
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A simple, convenient, economical method of giving the infant its daily quota of the essential antirachitic vitamin is provided in Drisdol—pure crystalline vitamin D₂—in Propylene Glycol.

Simple—Convenient

Just add Drisdol in Propylene Glycol to the milk or milk formula. Perfect dispersion results immediately without affecting the taste or odor of milk to even the slightest degree.

Fully Utilized—Economical

Drisdol neither floats nor adheres to the bottle. Therefore, nothing is lost, the full dose is utilized.

Moreover, the daily dose is small—2 drops in milk for infants, and from 4 to 6 drops in milk for children or adults.

How Supplied

Drisdol in Propylene Glycol—10,000 units per Gram—in bottles of 5 cc., 10 cc. and 50 cc., with a dropper delivering 250 U.S.P. vitamin D units per drop.

DRISDOL®
IN PROPYLENE GLYCOL

Specifically

a Good Start

CARTOSE in the Infant's Formula

Widespread clinical experience has established Cartose as a carbohydrate of choice in the infant's diet.

"Spaced" Absorption

Cartose—liquid carbohydrates—is a mixture of dextrans, maltose and dextrose. Dextrose is available for immediate absorption; maltose is first split to dextrose while dextrin passes through two steps—conversion to maltose, followed by change to dextrose—before assimilation.

Reduced Fermentation

Cartose—by providing this "spaced" absorption of carbohydrates—reduces possibility of gastro-intestinal distress due to excessive carbohydrate fermentation.

Rigid Sanitary Manufacture

Cartose is manufactured under the most exacting conditions of cleanliness. The manufacturing process itself is sterilizing.

Cartose contains no added flavoring, cane sugar or preservative.

Compatible

Cartose is suitable for use with milk in any form (fluid, evaporated or dry). Usual daily dose is 2 to 4 tablespoonfuls incorporated in feedings. Bottles of 16 oz. 60 calories per tablespoonful.

CARTOSE®

MIXED CARBOHYDRATE LIQUID

for Babies

Winthrop-Stearns INC.

NEW YORK 13, N. Y. WINDSOR, ONT.

NEW DRISDOL®
WITH VITAMIN A in (Sesame) Oil
NOW Also Milk Dispersible
Contains 50,000 U.S.P. units of Vitamin D₂
U.S.P. units of crystalline Vitamin A
(calciferol) per gram. 1250 U.S.P.
units of Vitamin D₂ per drop.
Dose same as Drisdol in Propylene
Glycol.
SUPPLIED in bottles of 10cc and 50cc.
Cartose and Drisdol trademarks reg U.S. & Canada.

Good! all these ways



direct from the spoon



mixed with cereal,
milk or juices



in infant's formula



For appeal plus adaptability, try Vi-Daylin—
the liquid vitamin supplement with the citrus-like flavor and
odor. Each honey-like 5-cc. teaspoonful contains the
minimum daily requirement of vitamin A for a child 1 to 12 years
old, twice the minimum daily requirements of vitamins C,
D and thiamine, and supplemental amounts of riboflavin and
nicotinamide. Vi-Daylin is stable at room temperature for two
years, won't curdle milk, won't stain clothing, leaves no fishy
after-odor. Supplied in bottles of 90 cc., 8 fluidounces and 1 pint.

ABBOTT LABORATORIES, North Chicago, Illinois.

VI-DAYLIN

TRADE MARK

(Homogenized Mixture of Vitamins A, D, B₁, B₂, C and Nicotinamide, Abbott)

from head to toe

CEREVIM-fed children showed greater clinical improvement, in the following nutrition-influenced categories, than children fed on ordinary unfortified cereal or no cereal at all:¹

- hair lustre
- recession of corneal invasion
- retardation of cavities }
condition of gums
condition of teeth
- skin color
- skeletal maturity }
skeletal mineralization
- *blood plasma vitamin A increase }
- *blood plasma vitamin C increase }
- subcutaneous tissues
- dermatologic state
- urinary riboflavin output
- musculature
- plantar contact

Here's why: CEREVIM is not just a cereal.

Much more: CEREVIM provides 8 natural foods: whole wheat meal, oatmeal, milk protein, wheat germ, corn meal, barley, Brewers' dried yeast and malt — PLUS added vitamins and minerals.

CEREVIM

CEREALS + VITAMINS + MINERALS

1. "A Study of Enriched Cereal in Child Feeding" Urboch, C.; Mack, P. B., and Stokes, Jr., J. Pediatrics 1:70, 1948.

*Cerevim contains neither vitamin A nor C, but apparently exerts an A-and-C sparing effect attributed to its high content of predigested protein and major B vitamins.

M & R DIETETIC LABORATORIES, INC. • Columbus 16, Ohio

October, 1949

49-JC2 [S]

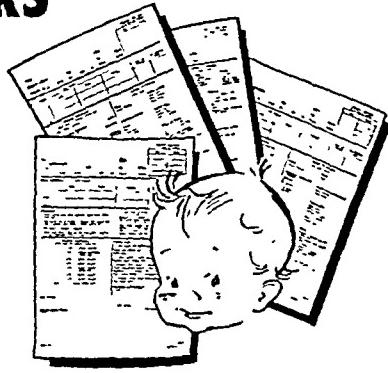
Page 7

HANDY TIMESAVERS FOR YOU!

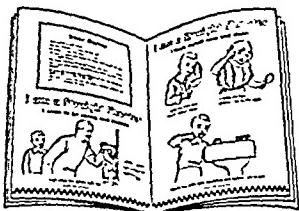
PEDIATRIC FEEDING DIRECTIONS

(birth to 3 mos., 3-6 mos., 6-10 mos., over 10 mos.)

Easy to use, complete, adaptable to individual patients. Help mothers follow your directions accurately. Each contains: formula or diet charts; food lists; food preparation methods; weight record; spaces for your directions, next appointment. Available in pads of 50 each, imprinted if desired.



ALSO... This GIFT for Your Young Patients



Eight-page book with pictures for the youngster to color. Written in primer style. Emphasizes health practices and other good habits you and the mother want the child to develop. Yours—to give your young patients.

Use this coupon for sample copies and a postage-paid order card. After examination, mail card to order in quantity.

NO COST OR OBLIGATION!

RALSTON PURINA COMPANY, Nutrition Service
9P-1 Checkerboard Square, St. Louis 2, Missouri

Please send the FREE material checked below:

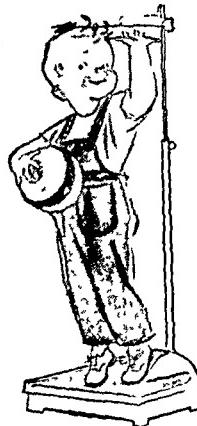
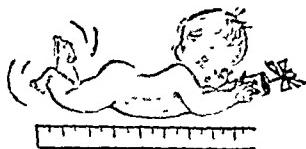
-C848 1 set Feeding Direction Forms
-C958 1 child's Color Book

Name _____ M. D. _____

Street _____

City _____ Zone _____ State _____

When Rapid Growth Calls For HIGH IRON and THIAMINE— Remember RALSTON!



Instant Ralston—enriched whole wheat cereal—is a rich source of iron and thiamine. A single 1-ounce serving supplies the following percentages of the minimum daily requirement:

	1-6 years	6-12 years	adults
IRON	113%	84.9%	84.9%
THIAMINE	84%	56%	42%
Plus 3.5 Gm. PROTEIN			



Instant Ralston supplies riboflavin and niacin, too . . . in taste-appealing, readily digested form.

Cooks in 10 seconds



SPREADS
like
ink
on a
blotter



New
efficiency
in
hypodermoclysis
and
local
anesthesia..
with
HYDASE
Trademark
Hyaluronidase



Injected solutions diffuse easily through
tissues treated with HYDASE.

A greater volume of fluid can be given
more quickly...with safety. Avoids
local swelling or pain due to distention.
HYDASE is also a valuable adjunct to
nerve block or infiltration anesthesia.
Completely non-toxic in therapeutic
doses.

Supplied: Sterile vials of 150 TRU (turbidity reducing
units)—the purest hyaluronidase preparation available.

WYETH INCORPORATED • Philadelphia 3, Pa.





GOOD EATING HABITS

should start in Infancy

Feed your baby from the beginning with foods which have appealing taste and meal time will be a happy time. A baby digests his food more easily when he enjoys it—gets the most benefit from it—and Beech-Nut makes food with flavor that babies enjoy.

Babies love them—thrive on them

Beech-Nut FOODS for BABIES

A complete line...

to meet the normal
dietary needs of babies.

PACKED IN GLASS

Beech-Nut high standards of production
and ALL ADVERTISING have
been accepted by the Council
on Foods and Nutrition of
the American Medical
Association.



Effective Anti-Arthritic Therapy

with

From laboratory dream to clinical reality—that's the story of Robins' new anti-rheumatic Pabalate, the unique combination of para-aminobenzoic acid and sodium salicylate which provides higher salicylate blood levels on lower salicylate dosage.

Now, further implementing the clinical value of this important new formula, Robins offers another outstanding research development: easily-administered, pleasant-tasting Pabalate Liquid! With Pabalate Tablets and Liquid, the physician can now more effectively treat patients with rheumatic fever or other rheumatic disease, at all age levels—from infancy to old age!

FORMULA: Sodium salicylate and Para-aminobenzoic acid (as sodium salt) of each, (5 gr.) 0.3 Gm. in each 5 cc. (1 teaspoonful) of a chocolate flavored liquid, or an enteric coated tablet.

INDICATIONS: Rheumatoid arthritis; acute rheumatic fever; fibrosis; gout; osteo-arthritis.

DOSAGE: Average adult dose: two teaspoonfuls or two tablets, three times daily.
Dosage for children proportional to age and severity of condition.

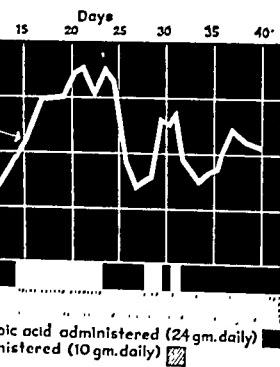
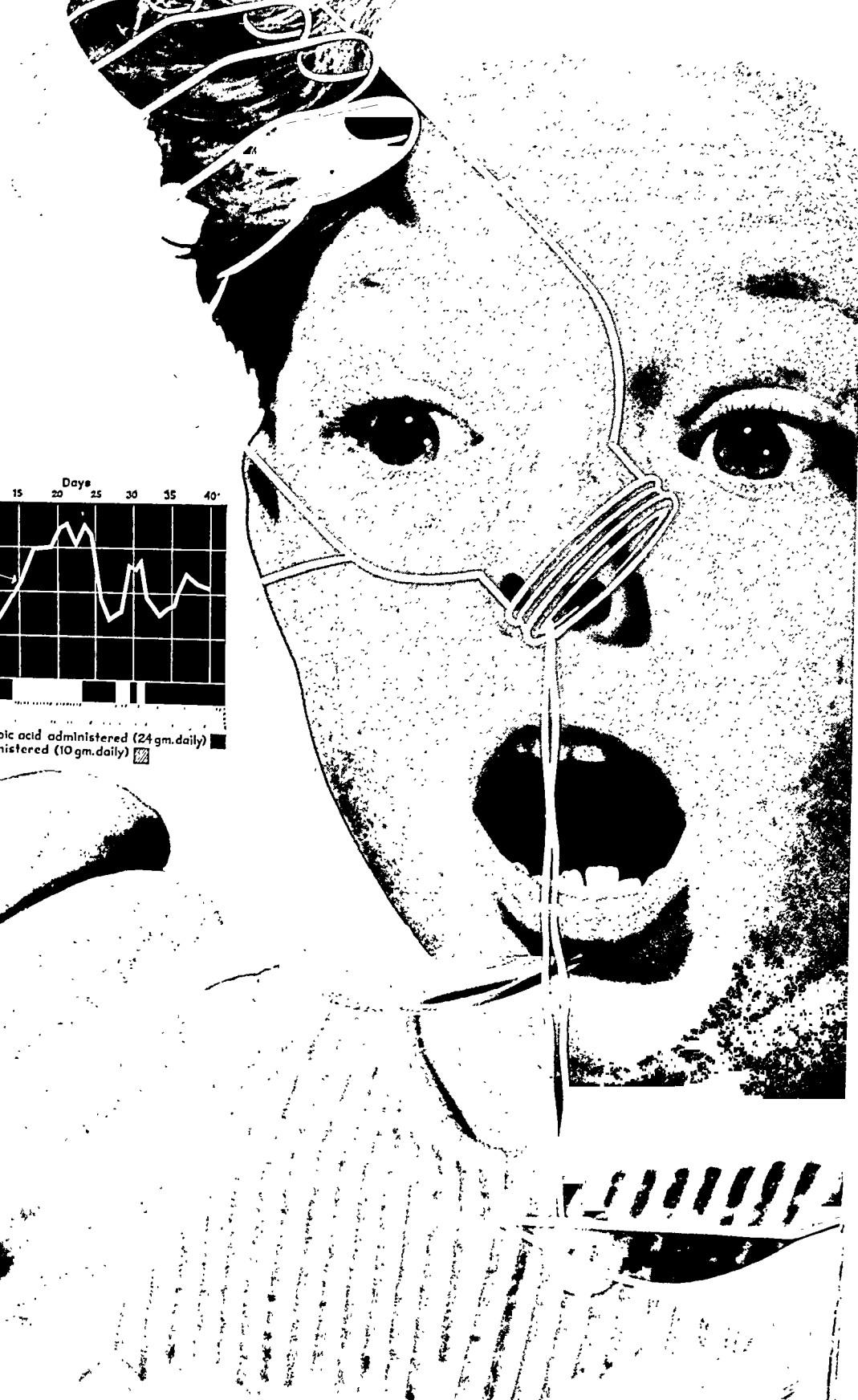
A. H. ROBINS CO., INC. RICHMOND 20, VIRGINIA
Ethical Pharmaceuticals of Merit since 1878

*For higher salicylate blood levels
on lower salicylate dosage—*



TABLETS AND LIQUID







the fluid sulfadiazine that's

...better tasting

...faster acting

To many patients—children, the aged and those with sore throats—swallowing bulky, half-gram sulfadiazine tablets is one of the discomforts of being sick. But these patients take ESKADIAZINE willingly. It tastes good.

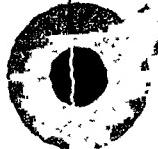
It is not thick and cloying; it is light and easy to swallow.

Each 5 cc. (one teaspoonful) of ESKADIAZINE contains 0.5 Gm. (7.7 gr.) sulfadiazine—the dosage equivalent of the standard sulfadiazine tablet. Yet desired serum levels are attained 3 to 5 times more rapidly with ESKADIAZINE than with sulfadiazine tablets. This is ascribed to the fact that ESKADIAZINE contains sulfadiazine in microcrystalline form.

Smith, Kline & French Laboratories, Philadelphia

Eskadiazine

the outstandingly palatable fluid sulfadiazine



"Our results with the molybdenum-iron complex have been...striking..."

Dieckmann, W. J. and Priddle, H. D.:
Am. J. Obst. & Gynec. 57: 541 (1949)

UNTIL recently Dieckmann has repeatedly reported that true hypochromic anemia of pregnancy did not respond satisfactorily to orally administered iron.^{1,2}

Now, however, following his latest investigation—a study of the value of molybdenized ferrous sulfate (Mol-Iron)—he states:

"We have never had other iron salts so efficacious in pregnant patients. Our results with the molybdenum-iron complex have been . . . striking . . . increases in hemoglobin were . . . dramatic and . . . rapid."³

This most recent evaluation of molybdenized ferrous sulfate (Mol-Iron) confirms the findings of all earlier investigators, who found Mol-Iron to be:

" . . . unusually efficacious . . . "⁴

" . . . a true example of potentiation of the therapeutic action of iron . . . "⁵

" . . . hemopoietically more active . . . "⁶

and remarkably well tolerated.^{5,7}

White's Mol-iron

MOLYBDENIZED FERROUS SULFATE

Tablets, Liquid

A highly palatable Liquid; ideal for infants and children. Presents a specially processed, co-precipitated, stable complex of molybdenum oxide 3 mg. (1/20 gr.) and ferrous sulfate 195 mg. (3 gr.) in each teaspoonful (4 cc.). Bottles of 12 fluid ounces; also Tablets—bottles of 100 and 1000.

1. Adair, F. L., Dieckmann, W. J., and Grant, K.: *Am. J. Obst. & Gynec.* 32:560 (1936).
2. Taito, P. J., and Dieckmann, W. J.: *Am. J. Obst. & Gynec.* 55:518 (1948).
3. Dieckmann, W. J., and Priddle, H. D.: *Am. J. Obst. & Gynec.* 57:541 (1949).
4. Neatly, E. R.: *Am. J. Med. Sci.* 212:76 (1946).
5. Hesly, J. C.: *J. Lancet* 66:218 (1946).
6. Chesley, R. F., and Annitto, J. E.: *Bull. Marg. Hague Maternity Hosp.* 1:68 (1948).
7. Keily, H. T.: *Penn. M. J.* 51:999 (1948).

White Laboratories, Inc., Pharmaceutical Manufacturers, Newark 7, N. J.
October, 1949

Delayed release...

Just as a great dam stores and releases water only as fast as the fertile lands below can utilize it, so does Alhydrox* adsorb antigens and release them slowly from tissue after injection. This gives the effect of continuous small doses.

Alhydrox is a Cutter exclusive—developed and used by Cutter for its vaccines and toxoids. It supplements the physician's skill by producing these immunizing advantages:

1. *Alhydrox selectivity controls the absorption of antigens, reducing dosage volume while building a high antibody concentration.*

2. *Alhydrox, because of its favorable pH, lessens pain on injection and reduces side reactions to a minimum.*

3. *Alhydrox adsorbed antigens are released slowly from tissue, giving the effect of small repeated doses.*

* Trade name for Aluminum Hydroxide Adsorbed

Specify these Cutter Alhydrox Vaccines

- Pertussis Phase I Alhydrox

30,000 mU on H pertussis per cc

- Tetanus Toxoid Alhydrox

- Diphtheria Toxoid Alhydrox

- Diphtheria Alhydrox

Cutter Diphtheria Toxoid plus 20,000 mU on H pertussis per cc for simultaneous immunization against pertussis and diphtheria

- Diphtheria Toxoid-Tetanus Toxoid Alhydrox

For simultaneous immunization against diphtheria and tetanus

- Dip-Pert-Tet Alhydrox**

Cutter diphtheria pertussis tetanus combined vaccine for simultaneous immunization against diphtheria pertussis tetanus

** Trade Mark

Your Cutter dealer has Alhydrox vaccines in stock

Alhydrox is exclusive with:

CUTTER LABORATORIES • BERKELEY 10, CALIF.

CUTTER

Kanana Banana Flakes

Reg. U. S. Pat. Off.

An ideal milk modifier for infants

Kanana Banana Flakes is a natural product containing all the food nutrients present in ripe bananas. As it is easily assimilated and very simple for mothers to use, it makes an ideal carbohydrate for fortifying milk mixtures for infant feeding. Note this simple procedure:

1. Prepare formula as usual.
2. Cool and pour into bottles.
3. Add Kanana Banana Flakes to each bottle, cap and refrigerate.
4. At feeding time shake bottle and warm to proper temperature.

One tablespoon of Kanana Banana Flakes contains 23 calories.

Below is given a typical 32 oz. formula.

Evaporated milk	12 oz.
Boiled water	20 oz.
Kanana Banana Flakes	8 tablespoons

Kanana Banana Flakes go into a stable suspension, and will pass readily through a nipple that has been enlarged with a hot needle. The Flakes will keep for months.

Kanana Banana Flakes cost less than fresh fruit.



The 5½ oz. can contains
20 six inch size bananas

Write for free samples



On sale at drug and grocery stores

KANNENGIESSER & COMPANY

76 NINTH AVENUE • NEW YORK 11, N. Y.

Distributed in Canada by
J. T. WAIT COMPANY, Limited, 760 St. Antoine Street, Montreal, Canada

October, 1949

Page 17

The Place

Prominent Hospitals

The Tests

Jergens Lotion against Usual
Hospital Skin Cares

The Results

Jergens Lotion Proved Indicated
Care for Baby Skin

Here are facts regarding baby skin care that should be of unusual interest to the profession:

An intensive series of tests has recently been completed in leading hospitals, under the guidance of staff pediatricians.

Jergens Lotion and three treatments commonly used in hospitals were tested on the skins of hundreds of newborn infants. The four treatments tested were:

1. Mineral Oil
2. Soap and Water
3. Cornstarch and Soap and Water
4. Jergens Lotion

The skins were observed for a period of two weeks for incidence of rashes: macules, papules, and pustules.

The results indicated that Jergens Lotion gave 5 times better protection against the skin irritations mentioned than the three other listed treatments.

You can recommend Jergens Lotion to your patients as a superior daily skin care for newborn infants.



Jergens Lotion is sterile, does *not* support bacterial growth. Active ingredients: Glycerine, Sweet Almond Oil, Spermaceti, Benzaldehyde, Gum Benzoin, Alcohol.

If you have not already received your copy of these Hospital tests, write to the address below and the report will be mailed to you promptly.
The Andrew Jergens Company, Box 6, Dept. 82A, Cincinnati 14, Ohio

now, better relief with...



a distinctive,
new, non-narcotic
antitussive-expectorant

At last, something really new in cough syrups . . . something completely rational . . . clinically sound . . . Robitussin 'Robins'. Robitussin employs glyceryl guaiacolate and desoxyephedrine hydrochloride, in a palatable aromatic syrup vehicle.

Glyceryl guaiacolate has proven an effective aid to expectoration, and a cough ameliorator with prolonged action, through its increase in and thinning of respiratory tract fluid;^{1,2,3} yet it has no ill effect upon digestion.¹

Desoxyephedrine's sympathomimetic action is also well recognized^{4,5,6}: by relaxing spasm of the bronchial musculature and helping maintain normal respiratory smooth muscle tone, it greatly minimizes the provocation of cough from spasm.⁵ At the same time it affords relief from psychic depression or a feeling of fatigue.

The syrupy vehicle, with its aromatic volatile oils, has a local demulcent effect. Furthermore, it assures patient cooperation by providing a base which makes Robitussin one of the most palatable of all antitussive-expectorants.

You will find Robitussin 'Robins' an exceptionally efficient, safe, therapeutic tool in the management of cough—for both adults and children.

Robitussin



FORMULA. Each 5 cc. (1 teaspoonful)

of Robitussin contains:

Glyceryl Guaiacolate . . . 100 mg.

Desoxyephedrine Hydrochloride . . . 1 mg.

In a palatable aromatic syrup.

DOSAGE. Children: one-half to one teaspoonful, according to age, three or more times daily.

Adults: one or two teaspoonfuls, as necessary every two to three hours.

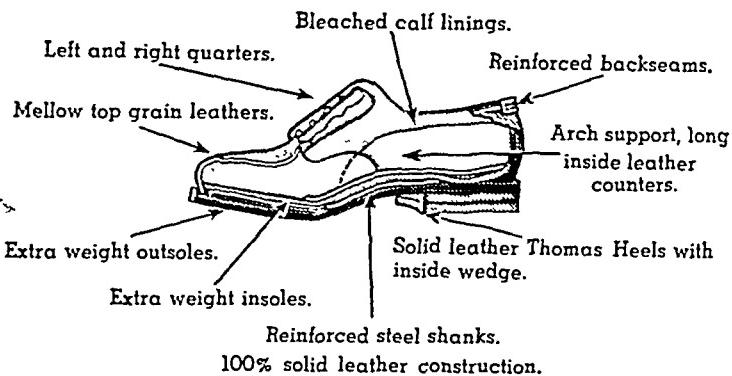
SUPPLIED Pint and gallon bottles.

REFERENCES 1. Connell, W. F. et al: Canadian Med. Assoc. J., 42:220, 1940. 2. Perry, W. F. and Boyd, E. M.: J. Pharm. Exper. Ther., 73:65, 1941. 3. Stevens, M. E. et al: Canadian Med. Assoc. J., 48:124, 1943. 4. Foltz, E. E. et al: J. Lab. Clin. Med., 28:603, 1943. 5. Graham, B. E.: Ind. Eng. Chem., Ind. Ed., 37:149, 1945. 6. Schulz, F. and Deckner, S.: Klin. Wochschr., 21:674, 1942.

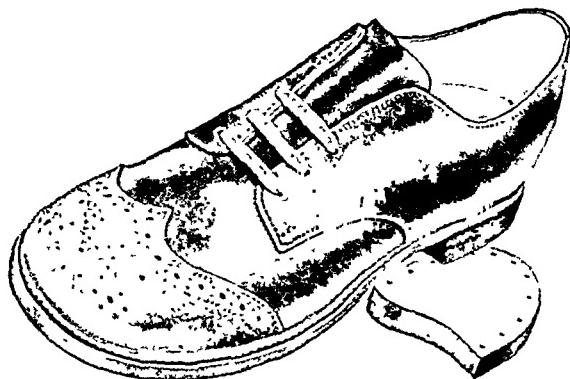
ROBITUSSIN—For Rational Cough Management

A. H. ROBINS COMPANY, INC.
RICHMOND 20, VIRGINIA
Ethical Pharmaceuticals of Merit since 1877

*Here is the
"INSIDE
STORY"
of why you can
recommend*



FLEET-AIR Correctives to your patients WITH ASSURANCE



**BROWN ELK
SCUFFLESS TIP OXFORD
STYLE 6007**

**FEATURING
THE FAMOUS
THOMAS HEEL**

QUALITY and scientifically correct construction, always discernible to the professional eye, are here revealed in this cutaway view of a *Fleet-Air* Correctives shoe.

Close to a half-century of making children's shoes exclusively has taught us secrets of design, methods of manufacture, that result in a corrective shoe of highest quality and exceptionally long wear. They are reasonable in price and sold only in selected stores.

So we urge you, Doctor, when parents ask you for the brand name of a reliable corrective shoe, to consider recommending *Fleet-Air* Correctives. We assure you that you would be making a wise recommendation.

Would you like to examine them for yourself? A postcard or letter will bring full information—or, if you prefer, our nearest Regional Representative will call at your convenience to explain . . . without obligation.

**Makers, also, of FLEET-AIR Normal Arch Health Shoes
EBY SHOE CORPORATION
EPHRATA 8, PENNSYLVANIA**

DECOSAL

SALICYLAMIDE COMPOUND
(DONLEY-EVANS)

DECOSAL provides the most potent salicylate compound, Salicylamide . . . as harmless as aspirin, yet has 2.08 times the analgesic potency of sodium salicylate and 7.5 times the analgesic potency of aspirin.

in an uncoated, crush-up tablet
or palatable liquid

RELIEF
without
REACTION

in rheumatic fever and arthritis

DECOSAL is singularly free from unpleasant gastro-intestinal side-effects common to the use of salicylates.

DECOSAL obviates untoward hematologic effects (hypoprothrombinemia) or depression of vitamin C levels encountered with large doses of salicylates.

and arthritis in providing prompt action and optimum absorption without unpleasant toxic or pro-thrombinopenic effects.

Literature and sample on request.

DONLEY-EVANS & COMPANY



ST. LOUIS 15, MISSOURI

Analysis Of 480 Cases Of Allergy Treated With Neohetramine

DIAGNOSIS	PATIENTS	% RELIEF (SLIGHT TO COMPLETE)
★ <i>Hay Fever</i>	171	86.0
★ <i>Allergic Rhinitis</i>	102	80.5
★ <i>Bronchial Asthma</i>	99	46.5*
★ <i>Atepic Dermatitis</i>	32	66.0
★ <i>Contact Dermatitis</i>	17	61.0
★ <i>Urticaria & Angio- Neurotic Edema</i>	47	80.5
★ <i>Migraine</i>	6	40.0
★ <i>Physical Allergy</i>	3	78.0
★ <i>G. I. Allergy</i>	3	66.6
TOTAL	480	

**Including effect
on children*

CONFIRMED BY CLINICAL EVIDENCE

"The side reactions obtained from Neoethetramine are definitely lower than those observed from the use of other drugs and therefore its use is safer in children." Crier, L. H., and Aaron, T.: *J. Pediat.* 34:414, April 1, 1949.

Cripe, L. H., and Aaron, T.: J. Pediat. 34:414, April 1, 1949.

"Its very low incidence of side actions makes it frequently a drug of choice."

Bernstein, T. B. & Feinberg S. M.: *J. Allergy* 19:393, Nov. 1948

TO BRING NEW SAFETY TO THE TREATMENT OF ALLERGIES

NEOHETRAMINE
TABLETS...SYRUP...CREAM **HYDROCHLORIDE**

Neoheteramine is the registered trademark of the Nepera Chemical Co., Inc., for its brand of Thonzilamine N, N-dimethyl-N' p-methoxybenzyl-N' (2-Pyrimidyl) ethylenediamine monohydrochloride.

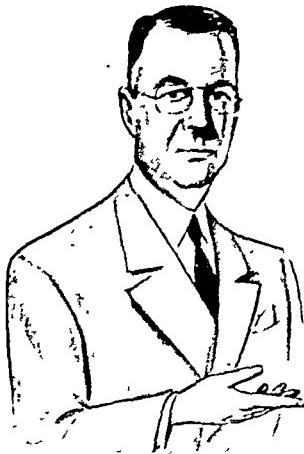
WYETH INCORPORATED, PHILADELPHIA 3, PA.



JUMPING-JACKS®

FLEXIBLE SHOES FOR HARD WEAR

...THE SHOE that lives up to
your RECOMMENDATION

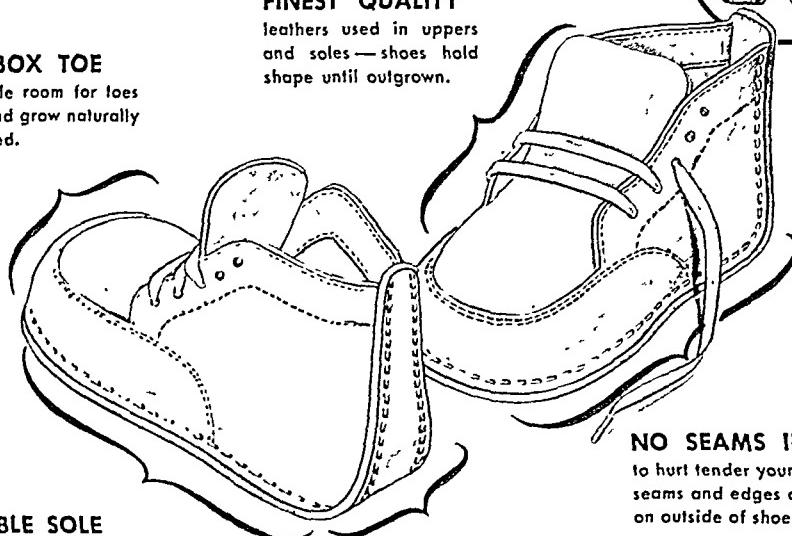
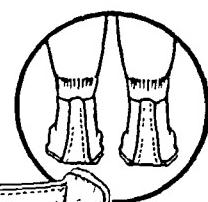


RAISED BOX TOE

insures ample room for toes
to spread and grow naturally
—unrestricted.

FINEST QUALITY

leathers used in uppers
and soles — shoes hold
shape until outgrown.



FLEXIBLE SOLE

permits natural foot action
without restraint, yet affords
necessary protection.

SQUARED HEEL

prevents foot from rocking.
Foot rolls straight forward on
ground contact.

NO SEAMS INSIDE

to hurt tender young feet. All
seams and edges constructed
on outside of shoes.



FOR ALL CHILDREN 6 MONTHS TO 4 YEARS

VAILSEY-BRISTOL SHOE COMPANY, INC.
ROCHESTER 3 - NEW YORK
MONETTE, MISSOURI - SKOWHEGAN, MAINE
MADE IN CANADA BY THE SAVAGE SHOE COMPANY, LIMITED - PRESTON, ONTARIO

A GREAT PAIR of SOAPELESS DETERGENTS



LOWILA

CAKE * LIQUID

When soap is taboo in DIAPER
RASH and INFANTILE ECZEMAS

LOWILA CAKE for skin cleansing

The only detergent cake which is entirely soapless yet cleanses as well as soap. No alkali whatsoever, pH approximates normal skin, never irritates. Less slippery than ordinary soap so mother can hold baby more firmly while bathing. Good lather.

LOWILA LIQUID for clothes
and household

Washes diapers, bedclothes, infant wear beautifully; soapless and nonirritant in proper dilution. Does not leave the alkaline, irritating residue left by soaps.



For SAMPLES and literature SEND COUPON

WESTWOOD PHARMACEUTICALS
Division of Foster-Milburn Company
468 Dewitt St., Buffalo 13, N. Y., Dept. J.P.

Convince me with TRIAL SUPPLY and literature
LOWILA cake and liquid

Dr. _____

Address _____



iron therapy without distress

Youngsters on ordinary iron therapy often feel as if they had swallowed a buzz saw. The nausea, vomiting, gastro-intestinal distress, diarrhea, constipation so often associated with the use of these preparations are eliminated when you prescribe Fergon, stabilized ferrous gluconate. It is usually so well tolerated^{1,2,3} by even your least iron-tolerant little patient that it may be prescribed before meals for maximum absorption. Because Fergon is better tolerated, better absorbed, better utilized, it meets the special needs of infants and growing children. Positive iron balance is quickly, pleasantly restored and maintained. Expressly for children—a palatable 5% elixir and 2½ grain tablets.

(1) Teeter, E. J. : *J. A. M. A.*, 127,973, Apr. 14, 1945. (2) Reznikoff, P., and Goebel, W. F. : *Jour. Clin. Investigation*, 16,547, July, 1937. (3) Tompsett, S. L. : *Biochim. Jour.*, 34,959, June, 1940.

®
Fergon
ferrous GLUCONATE

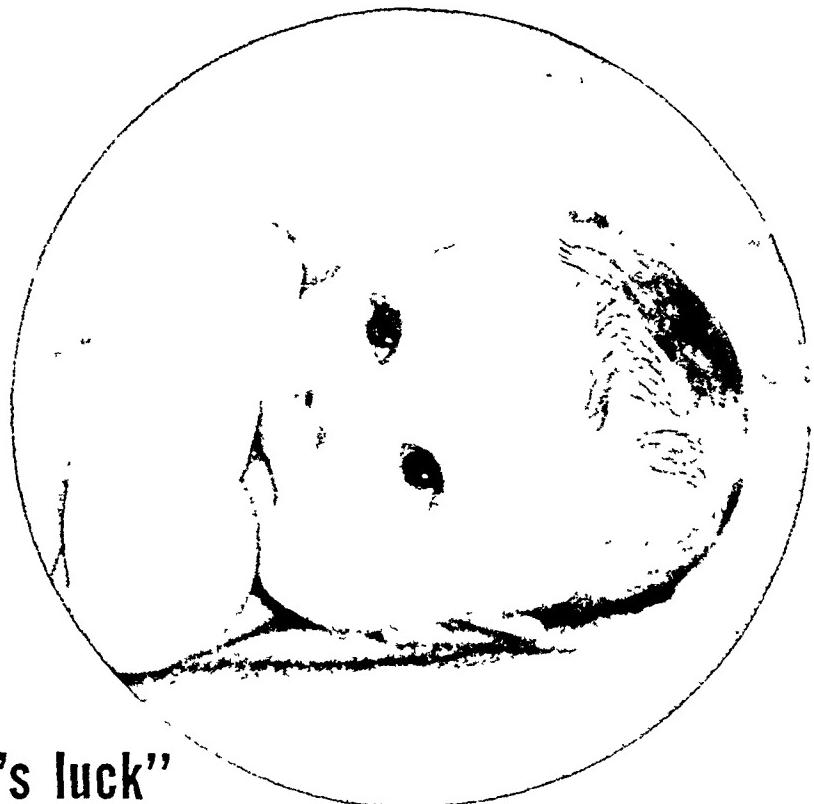
Winthrop-Stearns Inc.
New York 13, N. Y. Windsor, Ont.

October, 1949

408M(MCA)

Fergon, trademark reg. U. S. & Canada

Page 25



"Beginner's luck" isn't always good

The good luck so often attributed to beginners can't be counted on in infancy. Here the "beginners" often meet insurmountable obstacles which have raised the proportion of infant deaths within the first 30 days to 62.1% of the total infant mortality.* During this hazardous first month proper selection of the first formula is therefore of vital importance.

'Dexin' has proved an excellent "first carbohydrate" because of its high dextrin content. It (1) resists fermentation by the usual intestinal organisms; (2) tends to hold gas formation, distention and diarrhea to a minimum, and (3) promotes the formation of soft, flocculent, easily digested curds. 'Dexin' does make a difference.

*Vital Statistics—Special Reports· Vol. 25, No. 12, National Office of
Vital Statistics, Washington, D C (Oct. 15) 1946, p. 206.

'Dexin'
HIGH DEXTRIN CARBOHYDRATE
BRAND

Composition—Dextrins 75% • Maltose 24% • Mineral Ash 0.25% • Moisture 0.75% • Available carbohydrate 99% • 115 calories per ounce • 6 level packed tablespoonfuls equal 1 ounce • Containers of twelve ounces and three pounds • Accepted by the Council on Foods and Nutrition, American Medical Association.
'Dexin' Reg. Trademark



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in sulfonamide
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SULFADIAZINE

A COMBINATION OF SULFACETIMIDE,
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The superior clinical efficacy and enhanced safety of triple sulfonamide mixtures have been well established.

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Lehr¹ states that this new combination is "a highly satisfactory sulfonamide mixture because of its low toxicity, excellent tissue distribution and good therapeutic efficiency."

TRICOMBISUL:

Tablets of 0.5 Gm. containing 0.166 Gm. each of sulfacetimide, sulfadiazine and sulfamerazine in bottles of 100 and 1000.

¹ Lehr, D. To be published.

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Articles to appear in early issues of
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By J. Edmund Bradley, M.D., and Miles E. Drake, Ph.D., M.D., Baltimore, Md.

POLYOSTOTIC FIBROUS DYSPLASIA.

By Louis J. Hackett, Jr., M.D., Albany, N. Y., and William M. Christopherson, M.D., New York, N. Y.

MYOTONIA CONGENITA.

By Donald R. Hirsch, M.D., Joseph Dancis, M.D., and Richard S. Ward, M.D., New York, N. Y.

CONGENITAL CYSTIC DISEASE OF THE LUNG.

By Donald E. Cassels, M.D., James M. Fritz, M.D., and W. E. Adams, M.D., Chicago, Ill.

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INFECTIOUS MONONUCLEOSIS TREATED WITH CHLOROMYCETIN.

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INCIDENCE OF MYCOTIC INFECTIONS IN CHILDREN WITH ACUTE RESPIRATORY DISEASE.

By Frances C. Whitcomb, M.S., Albert Milzer, Ph.D., M.D., and Ralph H. Kunstadter, M.D., Chicago, Ill.

CRITERIA OF OPERABILITY IN TRICUSPID STENOSIS.

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AUREOMYCIN IN THE TREATMENT OF ACUTE BRONCHIOLITIS OF INFANTS.

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BRAIN TUMORS IN CHILDREN. I. GENERAL CONSIDERATIONS.

By A. Earl Walker, M.D., Baltimore, Md., and Theron L. Hopple, M.D., Toledo, Ohio.

THE PROGNOSIS OF FACIAL NERVE PARALYSIS IN POLIOMYELITIS.

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By Max J. Fox, M.D., and Bruce F. Grotts, M.D., Milwaukee, Wis.

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For the
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ABDEC® DROPS

contain adequate amounts of eight important vitamins in a clear, stable, non-oily and non-alcoholic solution that facilitates rapid absorption and thorough utilization.

Comprehensive multivitamin therapy is thus available

for the well child, as a routine measure to prevent vitamin deficiencies of even minor degree, resulting from common transitory aberrations of eating habits;

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ABDEC DROPS are supplied in 15 cc. and 50 cc. bottles with a calibrated dropper for accurate dosage. Each 0.6 cc. (10 minims) contains vitamin A, 5000 units; vitamin D, 1000 units; vitamin B₁, 1 mg.; vitamin B₂, 0.4 mg.; vitamin B₆, 1 mg.; pantothenic acid (as sodium salt), 2 mg.; nicotinamide 5 mg.; vitamin C, 50 mg.

ABDEC DROPS may be placed directly on the tongue or may be added to food or formula. Average daily dose (preferably given at a single feeding) is 0.3 cc. (5 minims) for infants under one year, and 0.6 cc. (10 minims) for older children.

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Elixir Thalfed is a valuable means of producing prompt and prolonged relief from the severe distress of asthma, and minimizing recurrence of paroxysms. It exerts a direct bronchial relaxing influence through the action of its contained aminophylline and ephedrine, and a central action by means of phenobarbital.

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Aminophylline.....	100 mg. (1½ gr.)
Ephedrine.....	20 mg. (1/3 gr.)
Phenobarbital.....	20 mg. (1/3 gr.)

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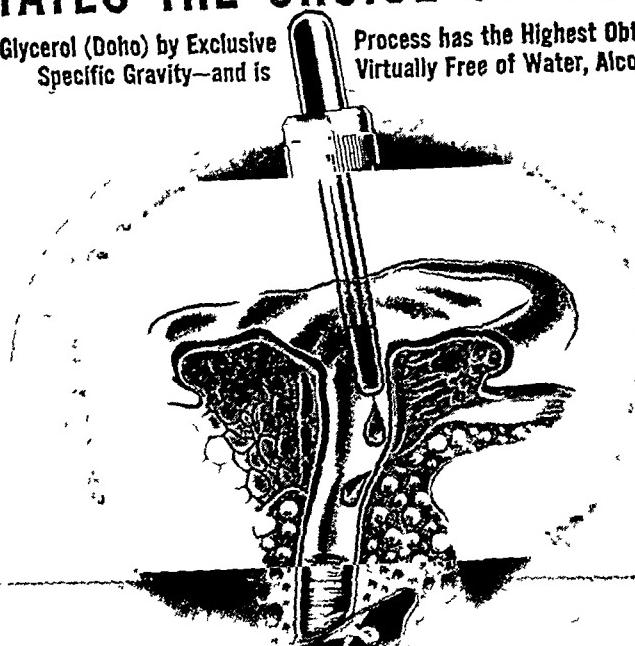


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THE INDICATION DICTATES THE CHOICE OF MEDICATION

Glycerol (DOHO) by Exclusive
Specific Gravity—and is

Process has the Highest Obtainable
Virtually Free of Water, Alcohol and Acids



IN ACUTE OTITIS MEDIA
REMOVAL OF IMPACTED CERUMEN
AS AN ADJUNCT TO SYSTEMIC ANTI-
INFECTIVE THERAPY, AS PENICILLIN, ETC.
CONTAGIOUS DISEASE EAR INVOLVEMENTS

USE *Auralgan*

...because its potent decongestant, dehydrating and analgesic action provides quick, efficient relief of pain and inflammation in any intact drum involvement.

FORMULA:

Glycerol (DOHO)..... 17.93 GRAMS
(Highest obtainable spec. grav.)
Antipyrine 0.81 GRAMS
Benzocaine 0.21 GRAMS

IN CHRONIC SUPPURATIVE
OTITIS MEDIA, FURUNCULOSIS
AND AURAL DERMATOMYCOSIS

USE

O-TOS-MO-SAN

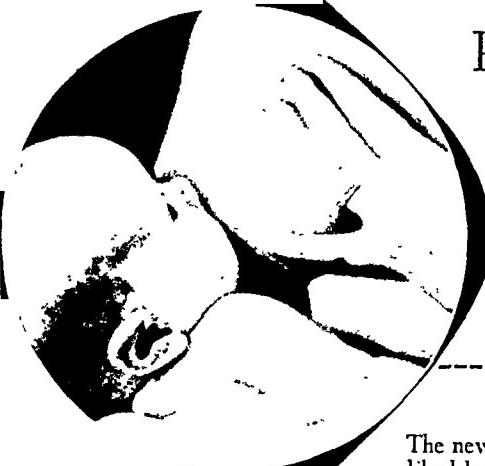
...a potent chemical combination (not a mere mixture), combining Sulfathiazole and Urea in AURALGAN Glycerol (DOHO) Base—because it exerts a powerful solvent action on protein matter, liquefies and dissolves exuberant granulation tissue, cleanses and deodorizes, and tends to exhilarate normal tissue healing in the effective control of chronic suppurative otitis media.

FORMULA:

Urea	2.0 GRAMS
Sulfathiazole	1.6 GRAMS
Glycerol (DOHO) Base	16.4 GRAMS

Literature and samples sent to physicians on request.

DOHO CHEMICAL CORP.—Makers of AURALGAN and O-TOS-MO-SAN NEW YORK 13



Plastishield technic of aseptic breast care approved by nursing mothers

The new Plastishield technic of postpartum breast care is well liked by patients. This fact is borne out by the reports summarized below:

50 patients 6 weeks to 6 months postpartum replied to a questionnaire as follows:¹

1. Are Plastishields comfortable to wear?
YES 90% NO 10%
2. Do Plastishields prevent soiling of clothes by milk leakage?
YES 88% NO 12%
3. Do Plastishields prevent nipple irritation?
YES 98% NO 2%

1,000 patients in 5 hospitals answered the same questions as follows:²

- | | | |
|-------------|---------|--------|
| QUESTION #1 | YES 91% | NO 9% |
| QUESTION #2 | YES 75% | NO 25% |
| QUESTION #3 | YES 98% | NO 2% |

Thus it will be seen that Plastishields encourage breast feeding because they:

1. Protect the nipple and areola from soreness and fissuring
2. Are conveniently and comfortably worn
3. Are characterized by greater cleanliness than other methods

Plastishield, inc. MINNEAPOLIS, MINNESOTA

¹ McKenzie, C. H.: The Use of Plastic Nipple Shields for the Lactating Breast, *Journal-Lancet*, 68:199 (May) 1948

² Abramson, M.: Breast Feeding the Newborn, *Gen. Practice Clinics*, (Oct.) 1947, p. 318.



Medical Authorities† Know This Fact:

NO DOCTOR CAN RECOMMEND ANY BETTER EVAPORATED MILK FOR INFANT FEEDING

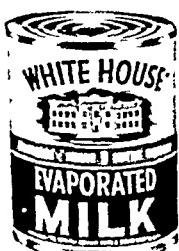
1. **WHITE HOUSE MILK** comes exclusively from tested dairy herds.
2. Processing of the milk is rigidly controlled under the most modern and sanitary conditions at the spotless White House Milk plants.
3. Many thorough quality and laboratory tests are made: before acceptance of the raw milk, at each stage of production, and after sterilization.
4. Repeated analysis of uniformity, sterility and vitamin D adequacy insure that White House Milk conforms to the very highest quality standards.



WHITE HOUSE MILK

There's None Better

400 U.S.P. Units of Pure Crystalline Vitamin D₃ Per Pint
Satisfaction Guaranteed by A&P or Your Money Back.



*Not Connected With Any
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*This statement is accepted by the American Medical Association's Council on Foods and Nutrition

External Cod Liver Oil Therapy

DESITIN OINTMENT

Contains Crude Cod Liver Oil, Zinc Oxide, Talcum, Petrolatum and Lanolin

Used effectively in GENERAL PRACTICE for the treatment of Wounds, Burns, Indolent Ulcers, Decubitus, Intertrigo, Skin Lesions, Hemorrhoids, Anal Fissures, etc.

In PEDIATRICS for the treatment of Diaper Rash, Exanthema, Chafed and Irritated Skin, caused by Urine, Excrements or Friction, Prickly Heat and in the nursery for General Infant Care.

Fatty acids and vitamins are in proper ratio, thereby producing optimum results. Non irritant, acts as an antiphlogistic, allays pain, stimulates granulation, favors epithelization. Under Desitin dressing, necrotic tissue is quickly cast off. Dressing does not adhere to the wound. In tubes 1 oz., 2 oz., 4 oz., and 1 lb. jars.

Desitin Medicinal Dusting Powder is super-fatted with crude cod liver oil in a non irritating powder base. Indications: In infant care in the treatment of IRRITATED SKIN, SUPERFICIAL WOUNDS, DECUBITUS, INTERTRIGO, PRURITUS and URTICARIA, in 2 oz. Shaker-Top Cans.

*Professional
Samples
on Request*



For the Medical Profession

DESITIN CHEMICAL COMPANY

70 SHIP STREET • PROVIDENCE • RHODE ISLAND

New Sulfa Combination...

TERFONYL

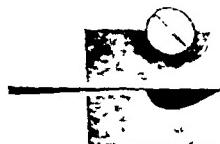
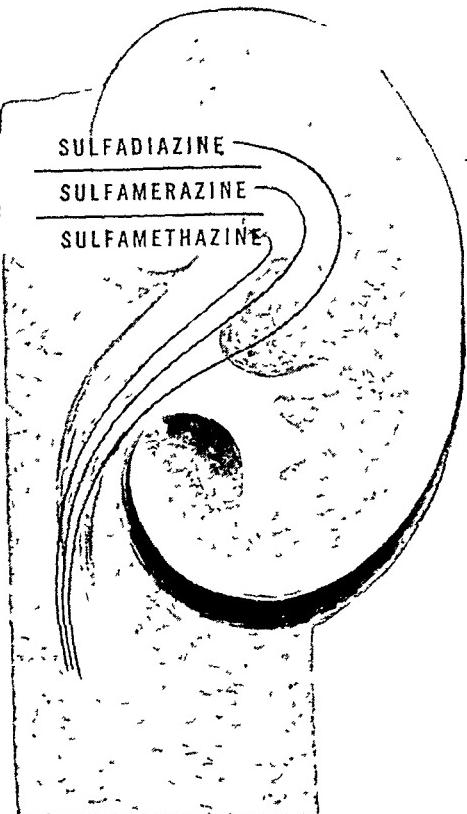
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HIGH BLOOD LEVELS

All three components are absorbed and excreted independently. High blood levels can be maintained without kidney concretion and with minimal sensitivity reactions.

WIDE ANTIBACTERIAL RANGE

All three components have a wide antibacterial range and are highly effective in the treatment of pneumonia and other common infections.



0.5 Gm. tablets
Bottles of 100 and 1000
Suspension, 0.5 Gm. per cc.
(pleasant raspberry flavor)
Pint bottles

"TERFONYL" IS A TRADEMARK OF E. R. SQUIBB & SONS

SQUIBB MANUFACTURING CHEMISTS TO THE MEDICAL PROFESSION SINCE 1858



Natural vitamins A and D . . . daily, for about a penny: In "drop-dosage" for infants or pleasantly-flavored Tablets for the older child. Vitamin D wholly derived from cod liver oil, vitamin A adjusted and standardized with fish liver oils. White Laboratories, Inc.

White's Cod Liver Oil Concentrate • LIQUID • TABLETS



AT LAST! EFFECTIVE RELIEF IN BRONCHIAL ASTHMA

—“inconspicuous side effects”¹

Prompt, complete relief in bronchial asthma and associated conditions . . . yet “causes very little central nervous stimulation and produces little or no pressor action.”¹

85%–90% effective relief in over 1400 patients during an exacting 8-year clinical study.

Increased vital capacity . . . better feeling of well-being . . . essentially free from undesirable side actions.

Its name is **NETHAPHYL®**

For liquid dosage . . . Syrup Nethaphrin.² Pleasant tasting Nethaphyl's effective relief, enhanced by Decapryl's long-lasting antihistamine action in seasonal and other allergies. Each 5cc contains Nethamine³ 25 mg., Theophylline (U.S.P.) 50 mg., Decapryl⁴ Succinate 6 mg.



Each capsule contains Nethamine³ Hydrochloride 50 mg., Butaphyllamine⁵ 0.12 Gm., and phenobarbital 15 mg. Also available in half-strength.



J-Henkel, E. K. Ann. Allergy, 5:397, 1947.

The Place of *Candy* in the Child's Dietary

Neither nature nor man has yet produced a food which can be eaten to the exclusion of all others and which can fully satisfy all nutritional requirements. Every food has its proper place when eaten in proper amounts and at the proper time.

Candies enjoy an established position in the child's dietary. Eaten at the conclusion of a meal, they satisfy the desire for a sweet, and add to the satiety value of the meal just completed. They contribute to the caloric needs of growing youngsters, which is not insignificant. Furthermore, the anticipation of a bit of candy as the last course not infrequently gives added incentive to eating the other foods comprising the meal.

That candies have a worth while place in the child's dietary is evident from the foods with which most candies are made—eggs, butter, cream, milk, fruit and nuts. To the extent these foods are present, candies contribute valuable protein, B complex vitamins, and minerals.



Council on Candy

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NATIONAL CONFECTIONERS' ASSOCIATION
ONE NORTH LA SALLE STREET, CHICAGO 2, ILLINOIS



NOW! on doctors'
recommendations



Babies get meat earlier than ever before!

The most significant change in infant feeding in recent years has been *earlier* meat-feeding, brought about by the development of specially prepared Meats for Babies, pioneered by Swift & Company. Almost overnight these clinically tested products, first of their kind, changed meat-feeding habits! Today, both pediatricians and general practitioners recommend these meats *months* earlier than they ever did before. Over a million babies are now thriving on Swift's Meats for Babies!

Swift's Strained Meats easy to feed earlier

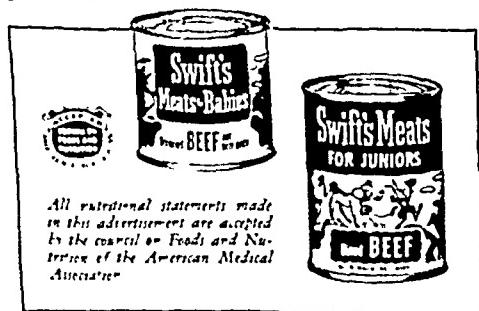
Soft, smooth Swift's Strained Meats are so fine in texture they may easily be bottle fed in the early weeks of life.

Some physicians start babies on these meats at two weeks—others as soon as the infant goes on solid foods.

Swift's Diced Meats—for older babies and young children—provide tender, bite-size pieces of meat that encourage chewing, aid teething. Swift's Diced Meats are tempting—help prevent anorexia in older babies. Six kinds: beef, lamb, pork, veal, liver and heart—help infants form sound eating habits.

Excellent source of complete proteins

Swift's Meats for Babies are an excellent source of complete, high-quality proteins . . . make available simultaneously all known essential amino acids—for optimum protein synthesis. In addition, Swift's Meats for Babies provide natural B vitamins and iron. As a food for growth and as a protective food meat has few peers. This is why so many doctors now recommend Swift's Meats for Babies for regular feeding early in life.



All nutritional statements made in this advertisement are accepted by the Council on Foods and Nutrition of the American Medical Association.

Special Note—In cases where infants are sensitive to milk protein, Swift's Strained Meats may be tolerated very well. In such cases, many physicians are recommending these meats be given in large quantities to replace milk protein in the infant diet.

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...foremost name in meats

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THE JOURNAL OF PEDIATRICS

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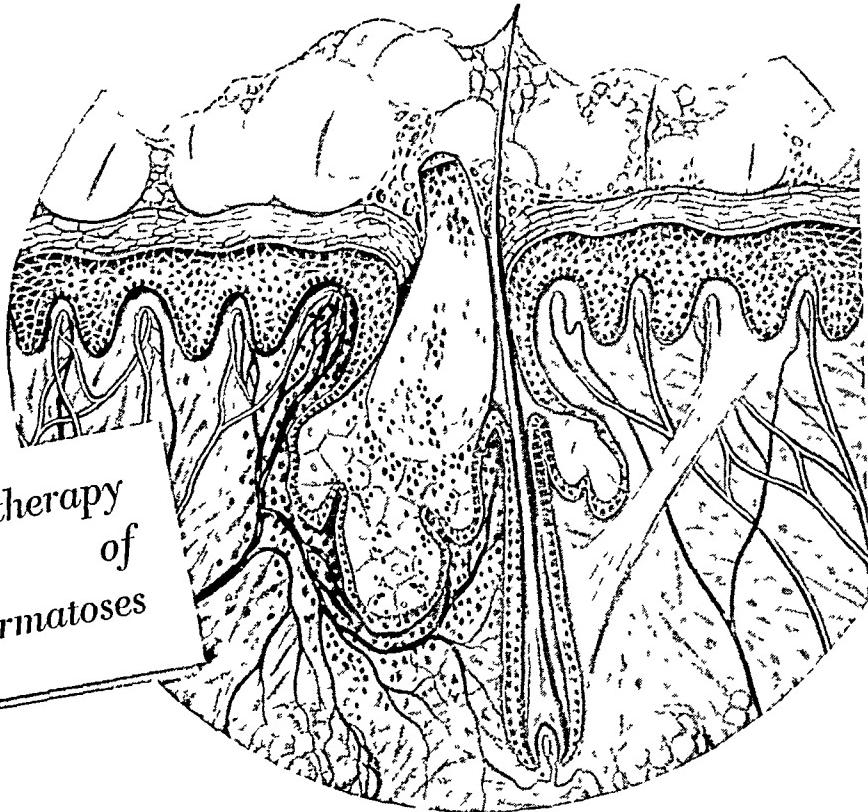
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in therapy
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This nonalkalizing, soapless, sudsing detergent cleans safely, effectively. Its pH value of 5.5 equals that of normal skin, thus leaving intact the protective "acid mantle." The lowering of surface tension and ease of use permit thorough, nonirritating cleansing. These are invaluable adjuncts in treating dermatoses where proper cleansing is essential to therapy.

pHisoderm is an emulsion containing ether sulfonate, lanolin cholesterol and petrolatum. Supplied in Regular, Oily and Dry Types, bottles of 2 oz., 7 oz., 12 oz., and 1 gal. and in 3 oz. refillable hand dispensers.

Winthrop-Stearns INC. New York 13, N.Y. • Windsor, Ont.

Adequate Breakfast AND FATIGUE DURING THE PRE-NOON HOUR

That the daily eating of adequate breakfasts lessens neuromuscular tremor during the pre-noon hour was recently shown in physiologic studies* conducted at the Departments of Physiology and Nutrition of a prominent medical college. As a direct consequence of the better nutritional state induced by improved breakfast habits, involuntary neuromuscular tremor is less during the last morning hour when 800 or 400 calorie breakfasts are the daily routine than when breakfasts are regularly omitted or coffee only constitutes breakfast.

Six young women graduate students were the experimental subjects in this carefully controlled scientific investigation. For permitting adequate physiologic adjustments to the four breakfast practices (800 calories, 400 calories, coffee only, and no breakfast), each practice was followed for a three-week period. The data obtained in the 800 calorie breakfast period were used as the standard base of reference.

Using specifically designed apparatus, the investigators determined the pattern of amplitude and rate of involuntary muscle tremor of the unsupported outstretched arm both before and after strenuous exercise. Measurements were made during pre-noon hours of the experimental periods.

Conclusions derived from this practically significant study follow:

1. When no breakfast was the morning

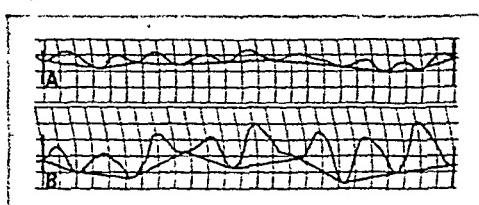
practice, the magnitude of muscle tremor substantially increased.

2. Habituation to coffee only for breakfast induced a similar increase in magnitude of muscle tremor.

3. Habituation to the 400 calorie breakfast after the coffee-only period markedly decreased the magnitude of muscle tremor; the tremor magnitude status tended to return to the status of the 800 calorie breakfast period.

The conditions of the study did not permit a direct comparison of the effects of the 800 and 400 calorie breakfasts on muscle tremor.

Health and nutrition authorities have long proclaimed the importance of daily adequate breakfasts in the promotion of good nutritional health. The results of this scientific study give direct experimental support to the soundness of such dictum.



Neuromuscular Tremor. Record of a normal tremor (A), and (B) exaggerated tremor. Subjects who are accustomed to eating breakfast have an exaggerated tremor when they suddenly begin to omit breakfast.



The presence of this seal indicates that all nutritional statements herein have been found acceptable by the Council on Foods and Nutrition of the American Medical Association.

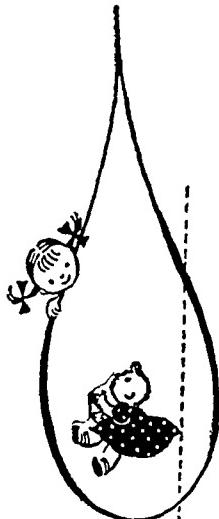
*Reprint of the research study and findings will be sent on request.



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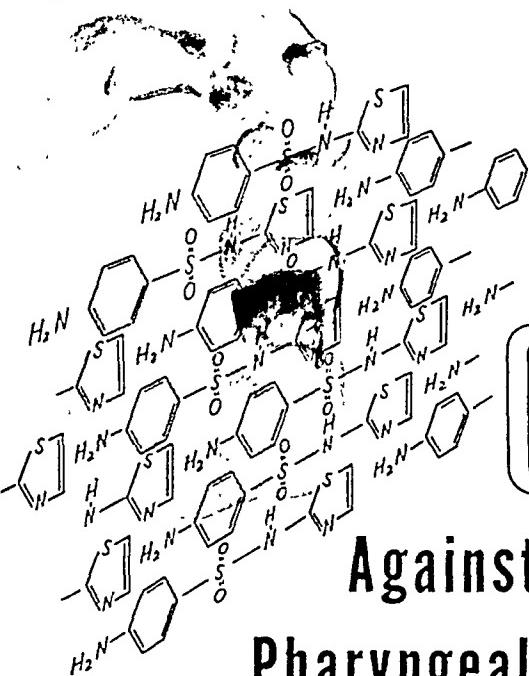
**The best years
of their lives . . .**

For almost a decade now they've had Vi-Penta Drops to help them grow. This pioneer water-miscible multivitamin drop preparation protects them in the rapid growth years with a generous supplement of vitamin C and members of the B complex, *in addition to A-and-D.* Vi-Penta Drops are freely miscible with milk and fruit juices. They are easily administered, well-tolerated and well-absorbed. Available in vials of 15 cc., 30 cc., and 60 cc.

HOFFMANN-LA ROCHE INC. • NUTLEY 10 • N. J.

Vi-Penta® Drops

'Roche'



C hemoprophylaxis Against Pharyngeal Infections

SAFE, TOPICAL METHOD

In Neiman's study* on chemoprophylaxis with White's Sulfathiazole Gum conducted over a 9-month period on 199 medical students:

1. The incidence of primary pharyngitis in the treated group was *less than half* that in the controls. A less marked, but statistically significant, decrease was also observed in the incidence of colds and irritational pharyngitis.
2. "It is worthy of note that the mouths of over 100 persons were exposed to the drug in concentrated form daily for eight months, *with no untoward effects.*"

As with the therapeutic use of Sulfathiazole Gum, the prophylactic application is safe because it is topical. In this series, for example, repeated examination of blood samples from unselected individuals in no case gave a positive test for sulfathiazole.

The dosage in these experiments was one to three tablets a day—an obviously economical procedure. No reactions were observed.

SULFATHIAZOLE GUM

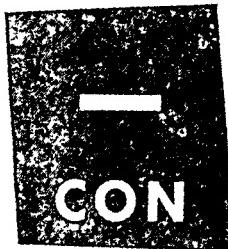
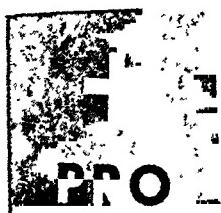
SAFE, TOPICAL CHEMOTHERAPY

Supplied in packages of 24 tablets— $3\frac{3}{4}$ grs.
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prescription boxes.

WHITE LABORATORIES, Inc., Pharmaceutical Manufacturers, Newark 7, N. J.

*Neiman, I. S.: Prophylactic Value of Sulfathiazole,
Archives of Otolaryng. 47:158-164 (Feb.) 1943.

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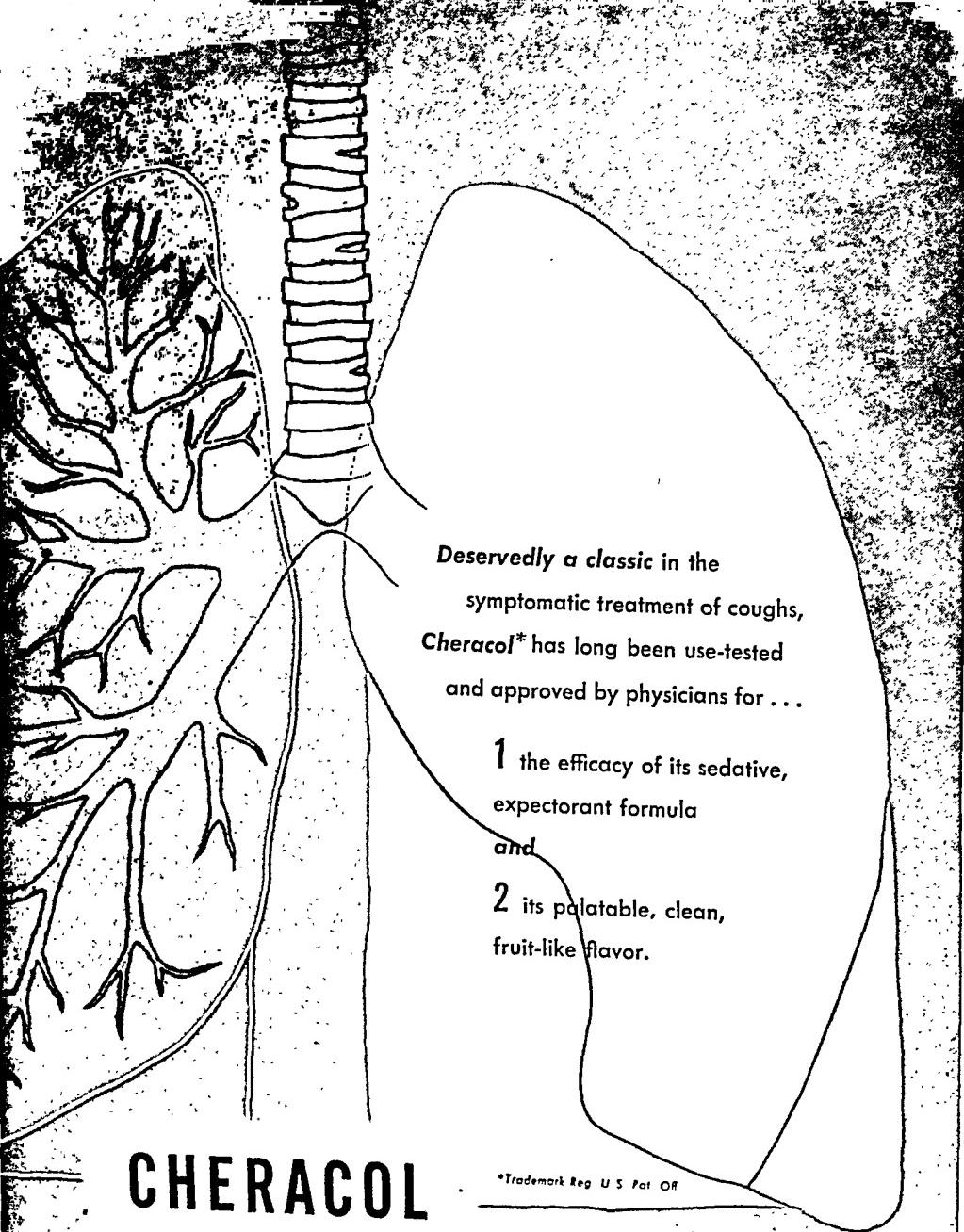
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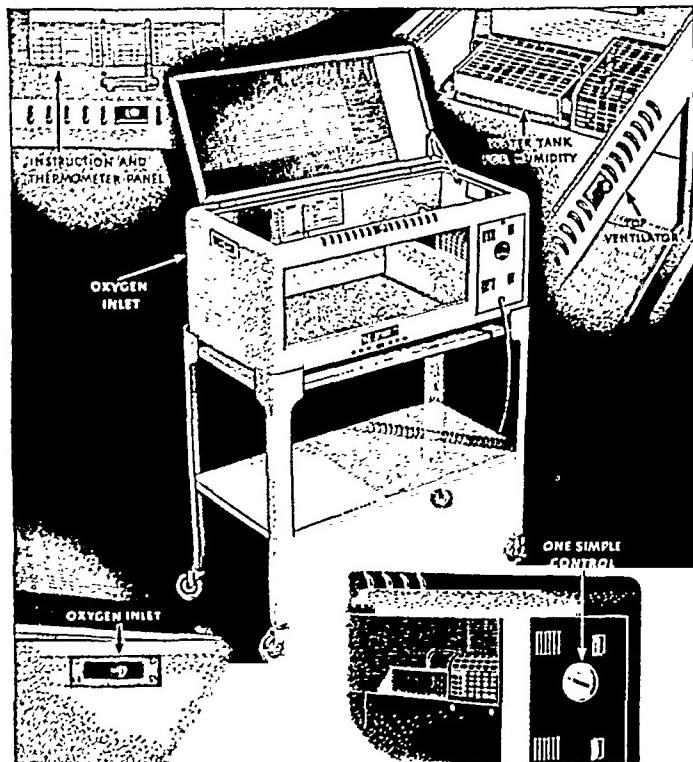
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Original Communications

TETRALOGY OF FALLOT

ANALYSIS OF FORTY-ONE CASES OF PATIENTS TREATED SURGICALLY AT THE UNIVERSITY OF MINNESOTA HOSPITALS

GEORGIA B. PERKINS, M.D.,* MARGARET M. HAMMOND, M.D., P. F. DWAN, M.D.,
AND M. J. SHAPIRO, M.D.
MINNEAPOLIS, MINN.

AT one time the achievement of the proper diagnosis of congenital abnormalities of the heart was of almost purely academic interest, serving little practical purpose other than to aid in the evaluation of prognosis in individual cases. Aside from its usefulness in differentiating such abnormalities from rheumatic carditis, its value to the patient was usually minimal. At present, however, as a result of notable advances in the surgical treatment of various types of congenital cardiac defect, added responsibility is placed on the physician, especially the pediatrician, to recognize their presence. The correct diagnosis is as important to the patient in terms of definitive treatment as identification of the causative microorganism is in an infectious disease. Increased interest in the problem of diagnosis has led to the development of a variety of special clinical techniques such as cardiac catheterization and roentgen ray studies following injection of contrast media, which furnish valuable confirmatory data.

Since the presentation in 1945 of a successful method for the surgical treatment of patients with tetralogy of Fallot by Blalock and Taussig,⁷ the correct diagnosis of this abnormality has become especially important. Concentration of interest on the subject has served to advance our knowledge regarding all types of congenital malformations of the heart.

The purpose of the present communication is to review the diagnostic findings and the results of treatment by means of the Blalock-Taussig procedure in forty-one tetralogy patients who were admitted to the University of Minnesota Hospital between September, 1946, and December, 1947. In four of these the thoracotomy was exploratory in character, no attempt being made to carry out the anastomosis; two patients expired during surgery, and the remaining thirty-five had the systemic-pulmonary arterial shunt constructed. The ages of the patients ranged from 18 months to 37 years, the

*From The Department of Pediatrics, University of Minnesota, Minneapolis, Minn.

All surgical Operations were performed by Dr. John R. Paine and Dr. Richard Varco of the Department of Surgery. A report of their surgical experience will be published elsewhere.

*Alpha Phi Research Fellow in Cardiology.

majority being between 6 and 8 years. The average age was 8.8 years. Four patients were 16 years of age. The operation was carried out on three of these.

ANATOMIC AND PHYSIOLOGIC CHARACTERISTICS OF TETRALOGY OF FALLOT

The tetralogy of Fallot consists of the following four abnormalities: (1) pulmonary stenosis with narrowing of the opening between the ventricle proper and the infundibulum; (2) interventricular septal defect; (3) dextro-position (with over-riding) of the aorta; and (4) right ventricular enlargement. The resulting symptoms of such abnormalities, namely, a high degree of cyanosis, dyspnea, faintness, possibly syncope, clubbing of the digits, polycythemia, and an increased oxygen capacity of the blood, occur in varying degrees.

CLINICAL HISTORY

Cyanosis is sometimes not present at birth, being noted first either at the time when the ductus arteriosus closes or when a relatively mild pulmonary or upper respiratory infection occurs during infancy; or it may not be noted until the activity of the patient is increased, for example, when he begins to creep. The ductus arteriosus is normally completely closed by the third month, although there is constriction or functional closure immediately after birth.²² Closure may be delayed even further and the duct may even remain patent. There may be reopening of the duct later in life. Why the ductus should close when it is a functioning structure is not known. Barklay and Salmon³ report that two out of ten operated patients were found to have a small open duct present. We have seen two patients, both about 3 years of age, in whom a machinery type murmur was found to have developed. Surgery was postponed in these cases until proper evaluation could be made as to the efficiency of the ductus in compensating for the defect. This observation should lead one to postpone surgery until the age of 3 years, if possible, so that any such compensatory attempts on the part of the body may be given an opportunity to be recognized. In the patients presented here, the onset of cyanosis was noted between the time of birth and 5 months in twenty-one cases (51.2 per cent); between 6 months and 2 years in fifteen cases (36.6 per cent); between 3 and 7 years in three cases (7.3 per cent); and two cases (4.9 per cent) the onset of cyanosis was uncertain (Table I).

Physical endurance was restricted in varying degrees, the distance which the patient could walk on level ground being used as a good clinical index. Eighteen (43.9 per cent) of our patients could walk less than one city block; fifteen patients (36.6 per cent) could walk from one to two blocks without exhaustion; five patients (12.1 per cent) had an endurance of three to six blocks; two patients (4.9 per cent) could go from seven blocks to one mile; and one patient (2.5 per cent) was able to walk more than one mile. Whether or not the patient suddenly feels exhausted and "squats" down in his tracks or feels fatigued but can walk into shelter or to a chair are also good indices.

TABLE I. SUMMARY OF CLINICAL HISTORIES AND PHYSICAL STATUS

HISTORY OR STATUS	%
Cyanosis first observed	51.2
Birth to 5 months	36.6
6 months to 2 years	7.3
3 years to 7 years	4.9
Indefinite	
Physical endurance (walking)	43.9
Less than 1 city block	36.6
1 to 2 blocks	12.1
3 to 6 blocks	4.9
7 blocks to 1 mile	2.5
More than 1 mile	
History of syncope or convulsions on exertion	36.6
Physical development	
Good	43.9
Fair	43.9
Poor	12.1
Occurrence of right aortic arch	21.9
Heart size	
Normal	41.5
Slightly enlarged	34.1
Moderately enlarged	4.9
Small	19.5

Syncope (or a convulsion) frequently occurs in those severely taxed. Fifteen of our patients (36.6 per cent) experienced this type of symptom. Seven of the ten patients studied by Barklay and Salmon³ had episodes of syncope. The patient's unwillingness to tolerate anything which interferes with free breathing such as thumb-sucking, removal of clothing over the head, washing the face, or blowing the nose, is an indication of his previous experience with and fear of the sensation of suffocation.

PHYSICAL EXAMINATION

The patient is sometimes undersized and may be somewhat emaciated. The degree of retardation in physical development corresponds approximately with the degree of circulatory deficiency. In the present study development was found to be "good" in eighteen patients (43.9 per cent), "fair" in eighteen (43.9 per cent) and "poor" in five (12.1 per cent). In our patients the degrees of cyanosis and clubbing of the digits were found to be directly related to the severity of the disease. Spinal kyphosis was frequently present.

The patient is usually very apprehensive, the smaller children showing complete dependence upon the parents. The aortic second sound in a small child is clearly audible in the second left interspace and may be interpreted as the pulmonic second sound. A normal sinus arrhythmia is the rule. Heart block occasionally results from the septal defect. This condition was not observed in any of our patients. The blood pressure is usually within normal limits, sometimes slightly low. The pulse pressures found here varied from 10 to 50 mm. of mercury, most frequently being between 20 and 30 mm. There is no unusual relationship between that of the arms and that of the legs. It is frequently very difficult to obtain the blood pressure, particularly the diastolic. The reason for this is obscure. Olin and Hughes¹⁶ found a very much elevated blood pressure in one of their two cases. Signs of embolism, cerebral or peripheral, were noted in three instances in the present series.

ROENTGEN EXAMINATION

On fluoroscopy the heart shadow is found to be somewhat widened, especially to the left, without marked cardiac enlargement. Of our cases, the heart size was found to be normal in seventeen patients (41.5 per cent), slightly enlarged in fourteen (34.1 per cent), more markedly enlarged in two (4.9 per cent), and small in eight (19.5 per cent). Unfortunately, the characteristic boot shape was not always obvious. As a result of the right ventricular enlargement a bifid apex may be seen with the notching at the apex indicating the right ventricle below and the left above, the pulsations in each being visible.

Although the arch of the aorta usually descends on the left side, it has been demonstrated that it descends on the right side in about one-fifth of the cases.²³ Nine of our patients (21.9 per cent) showed this abnormality. The importance of this lies in the fact that, since the innominate artery always lies on the side opposite to that on which the aorta descends, the side on which the incision for surgery may be made will depend upon where the vessel to be used for anastomosis lies. Thirty-two of the thirty-five anastomoses completed in our series of cases were made between the right or left subclavian artery and the right or left pulmonary artery, respectively. The innominate artery was used in but three cases.

Because of the decrease in pulmonary circulation, the pulmonary markings are found to be less marked than normal. Although not all of the patients in this series showed a high degree of decrease in the peripheral vascular pulmonary markings, every one showed some decrease in the size of the hilar vessels. The other important positive criterion is a small pulmonary artery and conus. We have found the decrease in pulsations of these vessels to be of more diagnostic aid than is the decrease in vascular markings, since the latter may sometimes be equivocal.

SPECIAL LABORATORY DATA

Laboratory findings are significant only in so far as they are characteristic of the disease and if they change in the postoperative state. A polycythemia was invariably present in these patients, the degree being roughly parallel to the degree of cyanosis and of hypoxemia. It has been found that, in contrast to the maintenance of a normal relationship between the volume of red cells and the volume of the plasma in polycythemia vera, the volume of the plasma in cases of cyanotic heart disease has been found to be below the expected level,²⁴ thus increasing the oxygen-carrying capacity of the blood at the price of increased viscosity. (Table II.)

TABLE II. SUMMARY OF DATA REGARDING BLOOD

	HEMOGLOBIN (GM. PER 100 C.C. BLOOD)	ERYTHROCYTES (MILLIONS PER CU.MM. BLOOD)	HEMATOCRIT (% R. B. C.)	OXYGEN SATURA- TION OF ARTERIAL BLOOD (%)
Preoperative	12.6-25.6	5.7-12.6	50-85	15.3-86.8
Postoperative	11.1-21.6	3.5-10.7	37-75	21.2-90.9

Taussig states that, in children, as long as the oxygen saturation of the arterial blood remains above 66 per cent, there is no need for and consequently is no stimulus leading to polycythemia.²² We have not always found this to be true in our series. However, we have found it true that the hematocrit reading tends to be lower in those patients with the higher oxygen saturation values. The preoperative hemoglobin values in our group varied from 12.6 to 25.6 Gm. per 100 c.c.; postoperatively they ranged from 11.1 to 21.6 Gm. (See Table II.) This represented a decrease of 0.5 to 9 Gm. in all of the cases studied and a decrease of from 1.9 to 9 Gm. in those with a good result, the average decrease of about 4 Gm. resulting.

The erythrocyte count preoperatively was found to be between 5.67 and 12.6 millions per cubic millimeter; postoperatively between 3.5 and 10.7. This represents a decrease of 0.2 to 4.6 million cells per cubic millimeter in all the patients and of 0.6 to 4.6 in those with a good result from operation, the average fall being about two million. The preoperative hematocrit values were found to be between 50 and 85 per cent, whereas postoperatively they were between 37 and 75 per cent. A decrease in reading of 4 to 20 per cent was found in all of the cases and of 6 to 20 per cent in those with good results, the average fall being about 13 per cent. The decreases in hemoglobin and hematocrit values occur more rapidly (one to three weeks) than the fall in the erythrocyte count, which takes from one to three months. This is in contrast to changes in the degree of oxygen saturation of the arterial blood, which changes almost immediately after establishment of the anastomosis.

Oxygen saturation studies are made both before and after surgery. This gives comparable results if the patient is under basal conditions. Therefore, the patient is given a relatively short anesthetic of Baird's solution (Pentothal Sodium and curare) rectally and intravenously when the arterial blood is drawn to prevent struggling and crying. The blood is obtained from the femoral artery. The method most commonly used for determining the oxygen content is that of Van Slyke.¹⁶ As will be noted later, evaluation of the exercise tolerance shows indications of being much more accurate. Since the degree of oxygen saturation decreases with voluntary exertion or crying, evaluation of exercise tolerance has been found to be easier from a mechanical standpoint and also to be more reliable.

In our series, preoperative oxygen saturation values of 15.35 to 86.8 per cent were found. Postoperative values of 21.2 to 90.9 per cent were found. Changes varied from -0.7 to +54.9 per cent in all patients having thoracotomies and between +1.2 and +54.9 per cent in those patients in whom a good result was obtained, the average change being from +10 to +25 per cent. In Taussig's²² series, the oxygen saturation values preoperatively were as low as 13 per cent and as high as 75 per cent and rose postoperatively to as much as 77 per cent, the majority of rises being from 20 to 50 per cent. The conditions under which these values were obtained, however, are unknown to us. In the cases of Barklay and Salmon² the average preoperative arterial oxygen saturation was 56.4 per cent; the average obtained postoperatively

was 80 per cent. The saturation never rises to the normal range of 94 to 97 per cent because of the over-riding of the aorta, an abnormality which, of course, persists after surgery.

There is a rise in the degree of oxygen saturation when a patient is allowed to breathe a high concentration of oxygen at basal conditions due to an increased oxygen content but with no change in the oxygen capacity. Such studies have recently been carried out in our laboratory, both preoperatively and postoperatively, by having the patient breathe 100 per cent oxygen after a sample of arterial blood has been drawn for determination of the degree of saturation, changes being measured by use of the Milliken-Smaller oximeter which is to be described shortly. The time necessary for the maximum saturation is noted and either a second sample of arterial blood is drawn or the percentage increase is indicated by the oximeter readings is recorded. We have found increases of 6 per cent to 15 per cent, but as yet an insufficient number of cases have been studied in this manner to justify drawing final conclusions.

In studies carried out during the surgical procedure, the increase was noted immediately following establishment of a shunt. The saturation times in ten of the patients on whom the test was performed ranged in preoperative times from ten to fifteen minutes, the normal range being about three to four minutes.¹¹ Postoperatively the values were within normal limits. Studies on three of Blalock's patients six months, one year, and two years postoperatively, respectively, also showed normal saturation times, although oxygen saturation studies with reference to their exercise tolerance still showed some limitations.¹¹ Burwell⁸ made the observation that the Eisenmenger's complex could be differentiated from the tetralogy of Fallot by the short saturation time in the former.

The Milliken-Smaller oximeter measures the oxygen content by recording electrically the varying photometric characteristics of the blood as determined by the relative contents of oxyhemoglobin and reduced hemoglobin as the blood flows through the lobe of the ear, the readings being obtained in terms of percentage change. The advantage of using this method of determining the degree of hypoxemia is that immediate and direct readings may be obtained under varying conditions as desired. Its use for this purpose has been reported elsewhere.¹¹

At the present time studies are under way to determine the effects of a standard amount of treadmill exercise on the percentage oxygenation of the blood, thus providing a more accurate and statistically comparable record of exercise tolerance. Decreases in oxygen saturation are noted and the time necessary for return to the original values is recorded (saturation time). In ten normal subjects, increases of oxygen saturation of one to 5 per cent were noted following this exercise, while definite decreases occurred in cyanotic patients. Too few patients have been tested as yet, however, to justify drawing final conclusions. There is good reason to believe that the comparative change in exercise tolerance after operation is more closely correlated with the clinical improvement of the patient than is the change in oxygen saturation levels. Two of the three patients of Blalock referred to previously showed

a 5 per cent decrease in saturation with "extended exercise."¹¹ However, preoperative values were not obtained. One patient reported from the Lahey Clinic had an oxygen saturation value fifteen days postoperatively which had fallen 5 per cent and seventy-five days postoperatively it had risen only 2 per cent from the preoperative value, although the clinical improvement was good. With the same exercise each time, the drop in oxygen saturation after exercise decreased from a preoperative value of 21 per cent to 9 per cent and then to 2 per cent in fifteen and seventy-five days, respectively.²⁰

The electrocardiogram typically shows a wide QRS amplitude, peaking of P and T waves, and marked right axis deviation. These abnormalities were present in all of our patients. Olin and Hughes¹⁶ reported one patient who had electrocardiographic evidence of coronary insufficiency.

It has been the opinion of some observers that many children with cyanotic congenital heart disease are mentally retarded. Contrary to this assumption, we have been impressed by the good, and in some cases, unusually good mental development shown. Psychometric examination made by Miss Audrey Arcola, clinical psychologist for the Department of Pediatrics, on thirteen of our patients picked at random, showed the following intelligence evaluation: low average, 4; average, 5; slightly above average, 1; and superior, 3. The oxygen saturation values in the "low average" group ranged from 49.9 to 86.8 per cent; in the "average" from 43.5 to 75.8 per cent; in the patient "slightly above average," 84.0 per cent; and in the "superior" group from 65.2 to 79.37 per cent. No correlation between the result of the psychometric evaluation and the preoperative oxygen saturation levels could be found.

Comparison of values for vital capacity, venous pressure, blood volume, and circulation time may be useful, but too few patients in this series had these determinations made routinely to justify attempts at correlation. Such data as bleeding time and clotting time, carbon-dioxide combining power of the plasma, blood urea nitrogen, and blood chloride levels are obtained preoperatively, both for evaluating the patients' ability to undergo surgery and as a base line for postoperative care. Blood, as well as nose and throat cultures, are taken, and appropriate preoperative chemotherapy is given if necessary to insure aseptic conditions in so far as possible. Dental examination and the preoperative removal of loose teeth has proved a helpful precaution, penicillin being used before and after extraction.

REGARDING SURGERY

While detailed discussion of the surgical procedures employed to ameliorate the circulatory dysfunction in tetralogy of Fallot is quite beyond the scope of this paper, brief comment on certain aspects of the problem is not inappropriate. Obviously, the question regarding the likelihood of the patient's being benefited significantly by operation should be considered of prime importance in determining the advisability of this form of treatment. Clinical judgment concerning the need for operation and risks involved can be bolstered by information regarding the degree of oxygen saturation of the ar-

terial blood, the patient's exercise tolerance, and the differential arterial pressures as measured directly by means of vascular and cardiac catheterization.

Preoperative preparation of the patient is of paramount importance. Adequate hydration before operation tends to obviate the necessity of having to administer fluids intravenously later on. This decreases the danger of cardiac dilatation and decompensation which may arise secondary to the establishment of the new shunt. Penicillin is given prophylactically in large doses for forty-eight hours before surgery as well as postoperatively. This is given in order that the blood stream may be rendered as free as possible from pathogenic penicillin-sensitive microorganisms, since the surgical anastomosis presents a favorable site for bacteria to collect. The other routine preoperative medications are morphine and atropine, the former being given in dosages indicated for the age. The atropine is given in relatively large but safe doses in order to depress the vagus nerve sufficiently to counteract its depressant effect on the heart when the latter is stimulated by unavoidable manipulation during the operation. The dosages in the present cases were 0.6 to 0.3 mg. for patients ranging in age from 6 to 13 years and 0.2 to 0.15 mg. for those patients who were younger than 6 years. Application of a local anesthetic to the vagus nerve at the time of surgery was used to magnify the effects of atropine.

The anesthetic found to be most satisfactory and the one which was used in the last twenty-six of our cases was the pentothal-curare solution described elsewhere by Dr. J. W. Baird² of the Division of Anesthesiology of the University of Minnesota. Administration of the solution is combined with intratracheal inhalation of 50 per cent nitrous oxide and oxygen. Cyclopropane and ether were used originally; however, four fatalities occurred under these inhalation anesthetics. To what extent anoxia or increased vagal stimulation accounted for these unfortunate results is not definitely known.

Since blood must flow after anastomosis from the systemic to the pulmonary circulation, operation is ineffective if the pressure in the latter system is too high. The maximum pulmonary arterial pressure used as a guide by the surgeons in our clinic has been that recommended by Blalock, namely, 30 cm. of citrate solution. In three of the cases reported here, however, the pressures were 31, 34, and 35 cm. of citrate solution, respectively. However, the results of operation on these patients were completely satisfactory. It is possible that the 30 cm. maximum pressure value can be revised upward for patients having systemic arterial pressures above certain levels.

POSTOPERATIVE CHANGES

A continuous murmur is usually heard postoperatively over the site of the anastomosis, sometimes appearing immediately following operation and at other times developing several days or weeks afterward. In nine of our patients it was first heard immediately postoperatively; in five it was heard later on the day of the operation. It was heard on the day following operation in three patients; on the third day in five; on the fourth in one; and on the fifth in two. In four other patients it was heard first on the sixth, seventh,

ninth, and twenty-first postoperative days, respectively. No murmur was heard postoperatively in seven patients. Of these, two had end-to-end anastomoses (one of the latter expired and the other had a result of questionable value) and three obtained no relief from their symptoms. The sixth patient in the group expired. The remaining one had a good result. Although the murmur is heard over the site of the anastomosis, it is often found to be louder in the back on that side. Occasionally, when no new murmur develops, the systolic murmur found previously is accentuated. The lack of a continuous murmur corresponds with the absence of a thrill over the anastomosis immediately after it is established. Even though a thrill is palpable below the clavicle after the chest has been closed, we have found that it may take some time for the murmur to develop.

The heart size increases in varying degree but not to an alarming extent. This increase is predominantly left ventricular. Although the enlargement begins almost immediately, the heart does not usually reach its maximal size until the end of the second week. Examinations as long as several months later in our cases showed no further increase in heart size. That the maximal degree of enlargement occurs almost immediately without change thereafter is not surprising. Lewis¹³ has shown that prolonged overwork does not cause cardiac failure and Palmer¹⁷ has demonstrated that cardiac enlargement in essential hypertension does not increase after the blood pressure has been stabilized. The vascularity of the lung field is moderately increased within a period of one to two weeks in most cases. The increase in the pulsations of the pulmonary vessels as seen on fluoroscopic examination is also indicative of the increase in pulmonary blood flow. The pulse pressures in our series of cases changed as a result of operation from -7 to +26 mm. of mercury, with an average of about 20 mm. increase. These changes are frequently not as great as might be expected with a shunt comparable with that in patent ductus arteriosus having been established. The changes show no constant relationship to the operative results.

COMPLICATIONS

In our experience *simple pleural effusion* was probably the most common postoperative complication encountered, the fluid occurring in significant amounts in 21 or 50 per cent of the patients. Thoracentesis for relief of respiratory embarrassment was required in three cases only. Cultures of the fluid removed were usually found to be sterile. One patient expired following removal of but 20 c.c. from a total of 1,900 c.c. of fluid in the chest. This death appeared to be due to a sudden shift of the mediastinum.

Chylothorax, occasionally resulting from damage to the thoracic duct when the left side of the chest is entered, is a more serious complication. It occurred in three patients in this series. All required repeated drainage. One was tapped seventeen times, yielding a total of 9.5 liters of fluid. While the mortality in general chest surgery complicated by chylothorax is stated to be as high as 50 per cent, all three of these patients survived.

The only therapeutic measure indicated in chylothorax other than thoracentesis and chemotherapy is that of maintaining normal levels of the various blood plasma constituents, such as proteins and electrolytes, by either the enteral or a parenteral route. *Hemothorax* occurred in two of our patients. One, which was massive and bilateral, was followed by death. The source of the hemorrhage was not adequately explained at autopsy, the anastomosis being unruptured.

Hornier's syndrome was found to be present shortly after surgery in four of our patients, the pupil of the eye on the operated side being the smaller of the two. This complication is doubtless due to the fact that superior cervical ganglion fibers proceed craniad via the plexus surrounding the internal carotid artery. Although the one case reported from the University of Texas showed no return to normal,³ ours did. One patient in our series showed ptosis and mitosis without changes in sweat secretion.

Hoarseness has been found to occur postoperatively by different observers. Although this may be the result of the intratracheal intubation only, it may also be the result of laryngeal or supraglottic edema, being sufficiently severe to require tracheotomy. This measure was necessary in one patient of the present series. Hoarseness may also be the result of temporary injury to the recurrent laryngeal nerve, should the latter take an aberrant course. Damage to the phrenic nerve is evidenced by diaphragmatic paralysis and by paradoxical diaphragmatic movement as demonstrated by fluoroscopy. This is also usually a temporary finding but is present in spite of the resorption of pleural fluid. We have observed the complication very frequently.

Hemiplegia may occur as a result of a deficient blood supply, especially if the innominate artery is used for the anastomosis. It may also be the result of an embolus. The hemiplegia may or may not be permanent. The arm on the side of the operative site remains cool for a varying period of time and it may be a matter of months before the temperature approximates that of the unoperated side, when a radial pulse may then become palpable. We had gangrene of the arm occur in one patient who later expired.

Other complications are less common. Empyema, mediastinal shift, pneumothorax, urinary tract infection, and prolonged lethargy each occurred but once among our cases. Thrombosis of the anastomosis occurred in one patient also and there was some question of its development in a second case. Cardiac decompensation was conspicuously absent in this series.

RESULTS OF OPERATION

The operative result was evaluated from both the clinical and laboratory standpoints, the patients' subjective improvement being included as an important criterion. A good result was obtained in twenty-six patients, or 74.3 per cent of those having anastomoses performed. One other patient obtained a fair result, two showed questionable results, and four showed no improvement. Of those having anastomoses completed, five died, giving a mortality of 12.1 per cent. The over-all mortality was 19.3 per cent, including deaths in patients who had exploratory thoracotomies without anastomoses and deaths

which occurred after the patient had been discharged from the hospital. Blalock and Taussig²⁰ had an over-all mortality of 21 per cent in their first 243 patients subjected to operation. Barklay and Salmon,³ in ten patients, had an over-all mortality of 20 per cent. Six of their patients were "much improved." Murray¹⁵ reported a mortality of only 7.3 per cent in 41 cases operated. His report does not elaborate on the types of patients or on procedures.

SUMMARY

The characteristic clinical, roentgenological, and laboratory findings in the tetralogy of Fallot type of congenital heart disease are discussed with particular reference to their occurrence in the patients studied at the University of Minnesota Hospital. Special attention is called to the use of the Milliken-Smaller oximeter for determining the arterial oxygen saturation with and without exercise both before and after operation for evaluation of the degree of circulatory improvement. The worthwhileness of using a standard exercise tolerance test as a method of determining the degree of work limitation both before and after operation is emphasized.

Advantages of using Baird's pentothal-curare solution for anesthesia and increased doses of atropine sulfate preoperatively, as well as local application of an anesthetic to the vagus nerve at the time of operation, are mentioned briefly.

Postoperative changes in the constituents of the blood and in the action of the heart are noted. The various postoperative complications and their relative incidences are listed and the over-all operative results in a series of forty-one cases are presented.

REFERENCES

- Abbott, M.: *Atlas of Congenital Cardiac Disease*, New York, 1936, American Heart Association.
- Baird, A. T.: *Pentothal Curare Mixture, Anesthesiology* 8: 75, 1947. *Pentothal Curare Solution: A Preliminary Report and Analysis of Its Use in 160 Cases, Anesthesiology* 9: 141, 1948.
- Barklay, H. T., and Salmon, G. W.: *The Blalock Taussig Operation*, J. PEDIAT. 31: 54, 1947.
- Best, C. H., and Taylor, N. B.: *Physiological Basis of Medical Practice*, ed. 3, Baltimore, 1943, William Wood & Co., pp 522-523.
- Blalock, A.: *Use of the Shunt or B_Y Pass Operation in the Treatment of Arterial Circulatory Disorders*, Ann Surg 125: 129, 1947.
- Ibid: *Physiopathology and Surgical Treatment of Congenital Cardiovascular Defects*, Bull. N. Y. Acad. Med. 22: 57-80, 1946.
- Blalock, A., and Taussig, H.: *The Surgical Treatment of Malformations of the Heart in Which There Is Pulmonary Stenosis or Pulmonary Atresia*, J. A. M. A. 128: 189-203, 1945.
- Burwell, C. S.: *Studies of the Circulation in Congenital Affections of the Heart and Their Application to Some of the Problems of Heart Disease*, Tr. College Physicians 10, 1942.
- Cassels, D. E., and Morse, M.: *Blood Volume in Congenital Heart Disease*, J. PEDIAT. 31: 185, 1947.
- Gilchrist, A. R.: *Surgical Aspects of Congenital Heart Disease*, Brit. M. J. 1: 515, 1946.
- Gullickson, G., Flan, J., Hammond, M., Paine, J., and Varco, R.: *Oxygen Studies in Congenital Pulmonary Stenosis*, Am. Heart J. 35: 940, 1948.
- Hawk, P. B., and Bergman, O.: *Practical Physiological Chemistry*, ed. 12, Philadelphia, 1947, The Blakiston Co.
- Lewis, J.: *Material Relating to Coarctation of the Adult Type*, Heart 16: 205, 1933.

14. Lundsgaard, C., and Van Slyke, D. D.: Cyanosis. Medical Monographs, vol. 2, Baltimore, 1923, Williams and Wilkins Co.
15. Murray, G.: Surgical Treatment of Congenital Heart Disease (Tetralogy of Fallot), Canad. Med. Assoc. J. 58: 10, 1948.
16. Olin, C. B., and Hughes, J. G.: The Blalock Operation for Congenital Pulmonic Stenosis, South. Surg. 13: 167, 1947.
17. Palmer, J. H.: The Development of Cardiac Enlargement in Disease of the Heart: A Radiologic Study, Med. Research Council Special Report Series, No. 222, 1937.
18. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry (Methods), Baltimore, 1932, Williams & Wilkins Company.
19. Potts, W. J., Smith, S., and Gibson, S.: Anastomosis of the Aorta to a Pulmonary Artery in Certain Types of Congenital Heart Disease. Case Rep. Child. Hosp. Chicago 5: 705, 1946.
20. Rutledge, D. I., and Adams, R.: Surgical Treatment of Congenital Heart Disease: Report of Case, Lahey Clin. Bull. 5: 89, 1947.
21. Taussig, H., and Blalock, A.: The Tetralogy of Fallot: Diagnosis and Indication for Operation; The Surgical Treatment of Tetralogy of Fallot, Surgery 21: 145, 1946.
22. Ibid.: Observations on the Volume of Pulmonary Circulation and Its Importance in the Production of Cyanosis and Polycythemia, Am. Heart J. 33: 413, 1947.
23. Taussig, H.: Congenital Malformations of the Heart, New York, 1947, Commonwealth Fund.

A CASE OF TETRALOGY OF FALLOT WITH A PATENT FORAMEN OVALE (PENTALOGY) SHOWING A MARKED LEFT VENTRICULAR HYPERTROPHY AND LEFT AXIS DEVIATION

BENJAMIN M. GASUL, M.D., JULIUS B. RICHMOND, M.D., AND
CECIL A. KRAKOWER, M.D.
CHICAGO, ILL.

BECAUSE the electrocardiographic demonstration of left axis deviation in patients with the cyanotic type of congenital heart disease has hitherto been considered diagnostic of tricuspid atresia,¹⁻³ we believe it significant to record a case of tetralogy of Fallot with a patent foramen ovale which presents a similar electrocardiographic picture.

CASE REPORT

A white girl, aged 9 years, was admitted to the University of Illinois Research Hospital with the following history: blueness of lips and fingernails since birth, puffiness of the face, hands, and feet during the previous week, and a dry, nonproductive cough for the previous month. She had been under constant medical care since birth. Eight days before admission to the hospital she awoke with edema of the face and two days later her hands, ankles, and feet also became swollen. Dyspnea on slight exertion, palpitation of the heart, and occasional dizzy spells with blurring of vision had been present since infancy. The family history was noncontributory. Her past history disclosed that she had chicken pox at the age of 8 years.

Physical examination revealed a dyspneic, cyanotic girl of 9 years, sitting in bed. Her temperature was 99.8° F., the pulse rate was 80, and the respiratory rate was 45 per minute. Her weight was 52 pounds; her blood pressure was 116/90. The skin was dry, scaly, and cyanotic. Marked edema of the feet, ankles, and sacrum was noted. There was no edema above the waistline. The mucous membranes, tympanic membranes, and finger and toenail beds were markedly cyanotic. There was marked clubbing of the fingers and toes. The lungs were clear on auscultation and percussion.

Cardiac enlargement was noted on percussion. The apex beat was in the sixth interspace in the anterior axillary line. There was a loud systolic murmur over the pulmonic area and at the apex. The abdomen was distended and the liver was palpable four fingerbreadths below the costal margin. The spleen and kidneys were not palpable. The following additional blood pressures were recorded: right arm 116/90, left arm 120/94, right leg 136/120, left leg 140/120. Ophthalmoscopic examination revealed hyperemic discs and slight retinal edema. The retinal veins were fuller and darker than normal.

The laboratory findings were as follows: the urine contained 2 to 3 plus albumin. Hemoglobin was 20.3 Gm. per 100 c.c., red blood count 9,220,000, white blood count 8,950.

The posteroanterior view of the chest (Fig. 1) showed a markedly enlarged transverse diameter of the heart, with the left border extending to the anterior

From the Department of Pediatrics and Pathology of the University of Illinois College of Medicine.

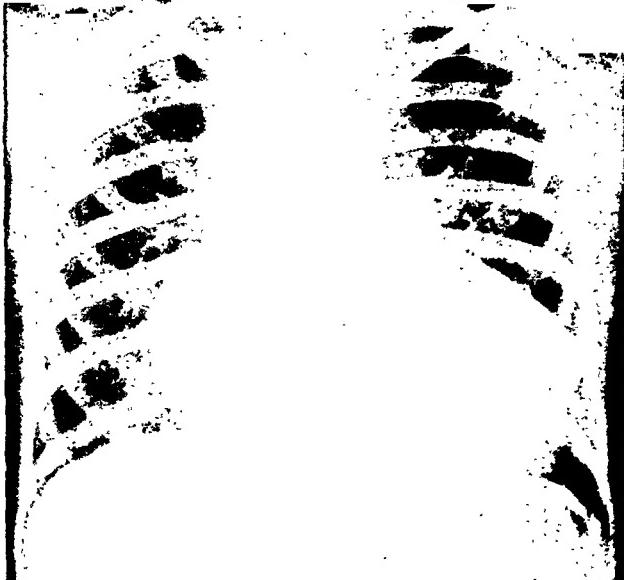


Fig. 1.—Posteroanterior view of the heart showing a mild enlargement at the transverse diameter with a concavity in the region of the pulmonary artery.



Fig. 2.—The left oblique view of the heart showing marked enlargement of the inflow tract of the left ventricle.

axillary line. There was a prominent concavity in the region of the pulmonary conus, and the pulmonary markings were somewhat more marked than normal.

The left oblique view (Fig. 2) showed a marked enlargement of the inflow tract of the left ventricle, with the latter not clearing the spinal column even on extreme rotation of the patient. The right auricle was also enlarged. Since the interventricular groove could not be visualized, it was difficult to determine the size of the inflow tract of the right ventricle.

The right oblique view (Fig. 3) showed a marked concavity in the region of the pulmonary conus.



Fig. 3.—The right oblique view of the heart showing a concavity in the region of the pulmonary artery.

The electrocardiograms showed sinus rhythm, left axis strain, and first degree heart block. The QRS was upright in Lead I and deeply inverted in Leads II, III and CF₄. The P-R interval was 0.26 second; the QRS 0.07 second. P₁ and P₂ were tall, broad, and peaked (Fig. 4).

Attempts were made to reduce the edema by means of Mercupurin. Fifteen days after admission, immediately after a meal, she complained of pain in her abdomen and before a physician could reach her bedside she expired. An autopsy was performed twenty hours after death with the following findings:

There was generalized marked postmortem lividity but no peripheral edema. There was clubbing of the fingers and toes. The peritoneal sac contained 35 c.c. of clear, straw-colored fluid. There were no adhesions. The heart weighed 330 grams (normal for this age, 115 grams). It was markedly enlarged and associated with some epicardial thickening with a fair amount of

fat. The right auricle was huge, measuring 6 by 7 cm. in external dimensions. When opened, it presented a large, patent foramen ovale measuring 1.5 cm. in diameter, mild parietal hypertrophy particularly close to the base of the auricle, and distention of the auricular appendage with pronounced thinning of the auricular wall between the pectinate muscles. The tricuspid valve measured 6.5 cm. in circumference and presented a number of friable small,

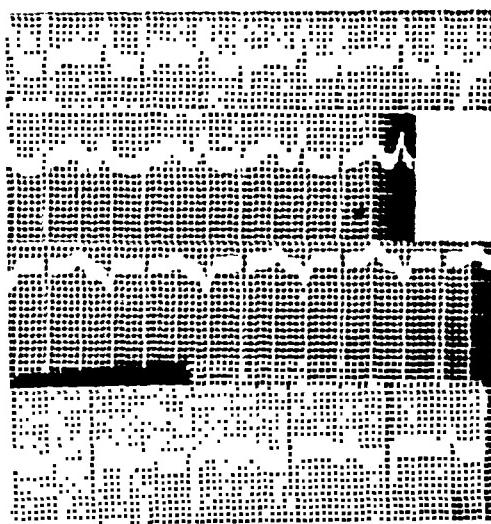


Fig. 4.—Electrocardiogram showing sinus rhythm, left axis strain, and first degree heart block.



Fig. 5.—Right view of heart exposing greatly enlarged right auricle with a widely patent foramen ovale.



Fig. 6.—Photograph showing enlarged, hypertrophic right ventricle with a stenosis of pulmonary valve and an interventricular septal defect. Contrast thickness of right ventricle with that of left.



Fig. 7.—View of left side of the heart with a greatly dilated ventricular cavity with hypertrophy of its musculature exceeding that of the right.

pale vegetations near its free border, the largest not exceeding 0.4 cm. in greatest diameter. The right ventricle was dilated and its columnae carneae and walls were markedly hypertrophied. The thickness of the walls of the right ventricle varied in different places from 0.3 to 1.0 cm. There was stenosis of the pulmonary valve with, however, a normal conus. This valve measured 1.2 cm. in circumference and was bicuspid and fused. There was an interventricular septal defect immediately below the stenosed valve, with smooth margins which measured 1.8 by 0.9 cm. The aortic valve was well to the right of the interventricular septum, somewhat to the right and posterior to the stenosed pulmonary valve. It measured approximately 4 cm. in circumference, and presented three cusps with some submarginal vegetations similar to those on the tricuspid valve. The left auricle was in all respects somewhat smaller than the right and presented very slight hypertrophy of its musculature near its base. The mitral valve measured 5 cm. in circumference and was entirely normal except for a row of small, recent, friable vegetations near its free margin. The left ventricle was enlarged and its walls hypertrophied. Papillary muscles and columnae carneae were not particularly hypertrophied, however. The thickness of the wall of the left ventricle varied from 0.3 cm. at the apex to 0.8 to 1.5 cm. elsewhere. The pulmonary artery was thin-walled and measured approximately 2.5 cm. in circumference. Right and left major trunks were normally distributed. The aorta gave off four trunks, viz. the right subclavian, right common carotid, left common carotid, and left subclavian arteries. The ascending arch of the aorta measured 4.5 cm. in circumference and its wall appeared to be somewhat hypertrophied but with excellent elasticity and no trace of atheroma. The same held true to some extent for the rest of the aorta. The coronary arteries arose normally from the aorta, pursued normal courses, and, on dissection, presented no pathologic changes. The ductus arteriosus was essentially a cordlike structure without a definitely patent lumen. The bronchial arteries were not dissected, nor were they injected to demonstrate their size.

Lungs.—Each weighed 120 grams (normal for this age 174 and 152 grams, respectively). They were a little smaller than normal. There was in both a relatively mild passive congestion and some edema.

Gastrointestinal Tract.—The stomach was markedly distended with air. The intestinal tract otherwise was profoundly congested.

The spleen weighed 100 grams (normal 73). The liver weighed 935 grams (normal 756). The combined weight of the kidneys was 170 grams (normal 165). All these organs showed passive congestion, which was particularly marked in the liver and pancreas. The brain was not examined. The heart's blood culture yielded no growth.

The only findings of interest microscopically were in the heart. The vegetations were of bland, nonbacterial type and were undergoing organization. These same sections of valves revealed considerable fibrosis, principally the result of older organization of thrombi associated in all with little vascularity but in one section with an area of calcification. In addition to hypertrophy of myocardial muscle fibers there were areas of fibrosis, both perivasculär and in that instance somewhat concentrically arranged, as well as irregular in outline and extent elsewhere in the myocardium. These latter in most instances probably represented healed areas of myocardial necrosis. There were rare, more recent necroses with cellular proliferation. Small, scattered foci of interstitial infiltration with polymorphonuclear and mononuclear cells were occasionally noted embedded in an edematous stroma.

Anatomical Diagnosis.—Diagnosis was tetralogy of Fallot with widely patent foramen ovale (pentalogy); nonbacterial verrucous endocarditis; focal

myocardial necroses (recent and old); interstitial myocarditis; passive congestion of viscera; ascites, mild; hydropericardium, mild.

COMMENT

Because of the unusual nature of this case, we believe it desirable to recapitulate our considerations prior to the death of the patient.

The history of cyanosis from birth, the marked polycythemia, and the clubbing of the fingers and toes definitely categorized this case as one of the cyanotic group of congenital malformations of the heart. The apparent enlargement of the left ventricle as demonstrated by fluoroscopic and x-ray examinations of the heart and confirmed by the electrocardiogram appeared to exclude the tetralogy of Fallot or a truncus arteriosus communis in which right ventricular enlargement is always present. A complete transposition of the great vessels could easily be excluded because children usually do not survive as long as our patient did with this malformation, and also because of the left axis deviation. In complete transposition of the vessels, the pulmonary markings should be prominent and one expects a definite narrowing of the base of the heart which widens in the left oblique view. None of these findings were observed. An isolated pulmonary stenosis was excluded because of the history of cyanosis from birth, and the left axis deviation. The vegetations noted on the valves were of the terminal, bland, nonbacterial, endocarditis type and of such a character that certainly with reference to the aortic valve there is no reason to suppose that they could have produced any insufficiency. The blood pressure readings also speak against this supposition. The myocardial necroses involved both ventricles. We, therefore, believed that the most probable diagnosis was a tricuspid atresia with an interauricular septal defect. We thought that the blood flowed from the right auricle into the left auricle through the interauricular septal defect, thence into the left ventricle and aorta and either into the pulmonary artery through the patent ductus, or into the right ventricle through an interventricular septal defect. Because the right ventricle in these cases is hypoplastic, the pulmonary artery would have to be stenosed, since a normal pulmonary artery cannot arise from a malfunctioning right ventricle. We explained the systolic murmur on the basis of either the pulmonary stenosis or interauricular septal defect.

The systolic murmur over the apex was considered to be due to either a relative mitral regurgitation resulting from an enlarged mitral ring, or as a murmur transmitted from the base. The apparent enlargement of the right side of the heart we believed to be caused by a markedly enlarged right auricle, and the tall, peaked P-waves appeared to substantiate this.

We were very surprised, therefore, when we learned from the autopsy that this was a case of tetralogy of Fallot with a patent foramen ovale. A search of the literature failed to disclose any case of tetralogy of Fallot with similar findings substantiated by autopsy. Brown, in his book on congenital heart disease, stated, "the finding of normal or left axis deviation in a cyanotic case should exclude a diagnosis of the tetralogy."¹¹ Maude E.

Abbott, in her *Atlas of Congenital Cardiac Disease*,² stated, "the roentgenogram in tricuspid atresia shows a left-sided enlargement that is characteristic and of diagnostic value, as is the left axis deviation seen in the electrocardiogram in these 'right-sided lesions' of the cyanotic group." Helen B. Taussig, in her book on *Congenital Malformations of the Heart*,³ states, "the electrocardiogram always shows a marked right axis deviation in Tetralogy of Fallot." Only Calo,⁴ in 1937, reported a case of what appeared clinically to be a tetralogy of Fallot with left axis deviation and a bundle branch block, but no autopsy was performed in this case.

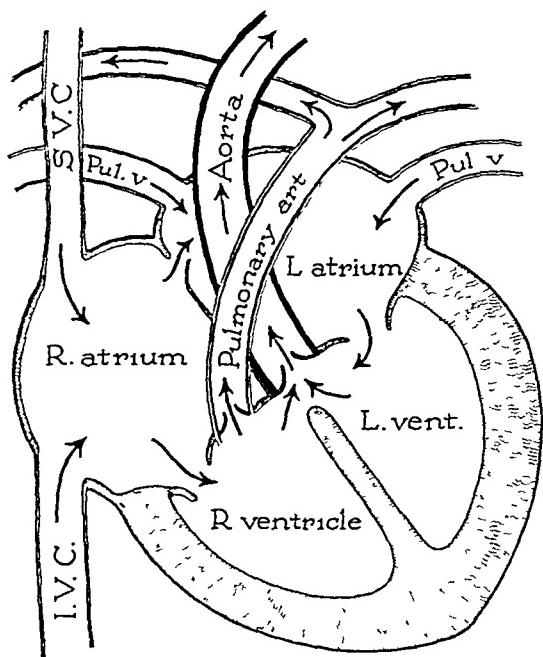


Fig. 8

In attempting to explain the left axis deviation and the marked hypertrophy of the left ventricle, we must conclude that the presence of the associated patency of the foramen ovale resulted in a shunt from the right to left side of the heart in this case (Fig. 8). The hemodynamics are probably very similar to that of a tricuspid atresia or stenosis. The pressure in the right auricle must have been higher than that in the left auricle and part of the blood probably flowed from the right into the left auricle, while the remainder flowed into the right ventricle. The additional blood flowing into the left auricle and thence into the left ventricle probably resulted in a gradual hypertrophy and dilatation of both of these chambers. The right ventricle in this case was also hypertrophied because of the stenosis of the pulmonary valve and the dextroposition of the aorta. We believe, therefore,

that a patent foramen ovale in association with a tetralogy of Fallot may in some instances result in hypertrophy of the left ventricle sufficient to produce a left axis deviation in the electrocardiogram.*

SUMMARY

The clinical and pathologic findings in a case of tetralogy of Fallot associated with patent foramen ovale are presented. It is believed that this is the first reported case of a tetralogy of Fallot with a hypertrophy of the left ventricle and a left axis deviation substantiated by autopsy.

REFERENCES

1. Brown, J. W.: *Congenital Heart Disease*, London, 1939, Staples Press Ltd., p. 152.
2. Abbott, Maude E.: *Atlas of Congenital Cardiac Disease*, New York, 1936, American Heart Association, p. 48.
3. Taussig, Helen B.: *Congenital Malformations of the Heart*, 1947, The Commonwealth Fund, p. 123.
4. Calo, A.: *Arch. d. mal. du coeur* 30: 805, 1937.

*Recently we have observed autopsies of two infants with Tetralogy of Fallot and patent foramen ovale whose electrocardiograms showed marked right heart strain. This suggests that the mere presence of the patent foramen ovale is not the determining factor in the production of a left heart strain. The blood must be shunted from the right auricle into the left one for a considerable length of time (probably a number of years) before the left ventricle hypertrophies and dilates.

THE USE OF CAROB FLOUR IN THE TREATMENT OF DIARRHEA IN INFANTS AND CHILDREN

ALAN E. SMITH, M.D., AND CARL C. FISCHER, M.D.
PHILADELPHIA, PA.

EARLY in 1948, following an unsatisfactory experience in the treatment of a series of infants with acute diarrheal disturbances, it was decided to follow the suggestion of a European pediatrician to test an antidiarrheic substance which has been used by European physicians in recent years but to the best of our knowledge has not been used in this country. The product, which is known commercially in Europe as "Arobon," is derived from the bean of the carob tree and contains added starch. Except for the use of this product, the therapy of the acute diarrheal disturbances in the infants to be reported here was not materially different from that previously used. It consisted of the commonly employed regime of an initial period of "starvation" during which water and electrolytes were administered by oral and parenteral means,¹⁶ followed by gradual increments in oral feeding.

Certain fruits and products prepared from them have been used for some years¹⁻⁷ in the treatment of diarrhea. Fully ripe apples and bananas, in particular, have been recommended and are available in the dried state in a number of preparations.⁸⁻¹² During the Spanish Civil War and at the beginning of the World War II, Ramos¹³ of Barcelona, Spain, faced with the increasing difficulty of procuring such dietetic products, sought other material for therapeutic use. He had noticed that during the war in Spain, the children of the poorer classes in Barcelona who ate the fruit of the carob tree had fewer diarrheal disturbances than did those of the wealthier classes. Based on this observation, he employed the dried pulp of the roasted carob mixed with starch for the treatment of diarrhea.

The carob^{14, 15} is the fruit of the carob tree, a leguminous plant which is native to the shores of the Mediterranean. This fruit is a bean-shaped pod, approximately 12 to 20 cm. long and 2 cm. wide. The pod contains a sweet pulp, pleasant to the taste; it is rich in sugar (more than 40 per cent) and low in protein (about 4 per cent). When dried, it furnishes a flour which remains in a fine suspension in water.

Carob pulp contains less cellulose and far less pectin than the apple or banana, but on the other hand it is very rich in lignin, a substance of a higher molecular weight than cellulose or pectin. The properties of lignin compare with those of pectin but differ considerably from those of cellulose. It is believed that the carob bean owes its unusual mechanical and disintoxicating properties to lignin.^{14, 15} Carob flour, distended with water, gives greater mass to the

From the Division of Pediatrics of The Hahnemann Medical College and Hospital of Philadelphia.

Material for this study has been kindly supplied by The Nestlé Co., Inc.

stools. The stools become dark brown in color, and, since they contain less water, dry increasingly rapidly as intestinal function returns to normal and their number diminishes.

The carob flour, as prepared under the name of "Arobon," contains 12 per cent added starch. Its taste is somewhat similar to that of cocoa, being pleasant only if the flour is sweetened with saccharin. The flour has the following composition:

Fat (ether extract)	0.5 per cent
Protein ($N \times 5.7$)	3.5 per cent
Soluble carbohydrate (sucrose and reducing sugars)	49.0 per cent
Other carbohydrate (hemicellulose and pectin)	22.0 per cent
Starch	13.0 per cent
Crude fiber	6.0 per cent
Minerals (ash)	2.5 per cent
Moisture	3.5 per cent
Calories	250 per 100 Gm.
1 oz. by dry weight equals	75 calories
1 tablespoonful equals	19 calories

METHOD OF STUDY

The plan of treatment included an initial period of "starvation," during which food other than water and electrolytes was withheld. In nineteen of the thirty infants in the study group, fluids were administered parenterally. In general, the plan recommended by Butler¹⁶ was followed. Plasma and blood transfusions were given to some infants, as were penicillin, streptomycin, and/or one of the sulfonamides. At the end of the "starvation period," approximately twenty-four to thirty-six hours, the carob flour formula was started.

For infants less than 6 months of age, the formula contained 2 teaspoonfuls of carob flour for each $3\frac{1}{2}$ oz. of water (5 per cent by weight). An average daily fluid intake of $2\frac{1}{2}$ to 3 ounces per pound of body weight was maintained. For infants more than 6 months of age, a more concentrated carob formula was used, the ratio being 4 teaspoonfuls of carob flour to each $3\frac{1}{2}$ oz. of water (10 per cent by weight). When the stools were well formed and dark brown in color, acidified powdered milk was added to the diet in the proportion of 2 teaspoonfuls to each $3\frac{1}{2}$ oz. of the carob flour mixture. If the milk was tolerated and diarrhea did not recur, the quantity of milk in the formula was increased and that of the carob flour decreased.

RESULTS

The data are summarized in Table I. Thirty infants, varying in age from 2 days to 15 months, with acute diarrheal disturbances were given the carob flour formula as part of their therapy. The formula was well tolerated even by the smallest infants. The effectiveness of the carob flour therapy was meas-

NAME	AGE	DIAGNOSIS	DAYS OF ILLNESS BEFORE ADMISSION OR START OF "AROBON"	NUMBER OF STOOLS ON DAY BEFORE ADMISSION	PRESENCE OF ACIDOSIS*
T.	4 mo.	Diarrhea, dehydration, congenital hypothyroidism	3	5	No
S.	4 mo.	Diarrhea	2	6	No
T.	4 mo.	Diarrhea, feeding problem, malnutrition, pneumonia	3	6	No
W. Baby C.	5 mo. 2 weeks	Diarrhea, vomiting, dehydration Allergy to milk	2 7	6 7	Yes No
M.	3 mo.	Diarrhea	3	5	No
di S.	4 mo.	Diarrhea, dehydration	2	9	No
P.	5 mo.	Diarrhea, malnutrition	2	3	No
W.	2½ mo.	Diarrhea, dehydration, bronchopneumonia	1	4	Yes
R.	1 mo.	Diarrhea	2	4	No
L., Jr.	1 mo.	Diarrhea, dehydration, bronchopneumonia	1	12	Yes
Baby J.	1 week	Diarrhea, dehydration, pneumonia	1	4	No
E. F.	3 weeks	Diarrhea, dehydration	4	5	Yes
Baby W.	2 days	Diarrhea, cleft lip, cleft palate	1	10	No
J.	7 mo.	Diarrhea, dehydration, malnutrition, eczema	4	8	Yes
G.	5 weeks	Diarrhea	2	9	Yes
V. B.	4 mo.	Diarrhea, double aortic arch	2	4	No
B.	5 mo.	Diarrhea, dehydration, feeding problem	3	6	Yes
K.	5 mo.	Diarrhea, tracheobronchitis	2	10	Yes
H.	2½ mo.	Diarrhea, tracheobronchitis	16	5	Yes
D.	2 weeks	Diarrhea, dehydration	3	8	Yes
R.	1 week	Diarrhea, dehydration	2	3	Yes
H.	1 mo.	Diarrhea, dehydration	3	8	No
R.	7 mo.	Diarrhea, dehydration	2	10	No
S.	14 mo.	Diarrhea, dehydration	3	3	Yes
M.	14 mo.	Diarrhea, dehydration	1	7	Yes
M.	2 weeks	Diarrhea, dehydration	5	12	Yes
Baby B.	1½ weeks	Diarrhea, dehydration	2	7	No
McK.	15 mo.	Diarrhea, dehydration, malnutrition, pneumonia	3	10	Yes
P.	2 weeks	Diarrhea, dehydration	3	11	Yes

*Criteria for diagnosis of acidosis: symptomatology, blood carbon-dioxide combining power, and urinalyses were evaluated.

†"Cure" means the achieving of formed stools and their remaining so after the addition of milk to the diet.

ured by the antidiarrheic action. Shortly after its administration, changes in the color, appearance, and consistency of the stools were observed. They became dark brown in color, homogeneous, and firm. In eleven infants the stools became formed ("earob stools") after one day of earob flour therapy (immediate effect); in twelve infants, after two days (rapid effect); in six infants, after three days (slow effect). In only one infant was there no antidiarrheic effect.

The effect on the weight curve was in more or less direct relationship to the condition of the stools. The average gain in weight was 6½ ounces.

Some of the infants regurgitated two or three sips of the earob flour formula after each feeding. Vomiting was never a serious factor, however, nor was it a sign of intolerance.

NUMBER OF S AFTER MISSION ACHIEVE CURE [†]	WEIGHT ON ADMISSION (LB.—OZ.)		WEIGHT ON DISCHARGE (LB.—OZ.)		NUMBER OF DAYS IN HOSPITAL	GAIN OR LOSS IN WEIGHT (LB.—OZ.)	RAPIDITY OF EFFECT FROM CAROB FLOUR	FLUID REPLACEMENT THERAPY
	4	6	13	7				
3	11	4	11	7	13	3	Rapid	Clysis
3	11	10	11	11	11	1	Rapid	
2	18	10	18	13	6	3	Immediate	Clysis
4	8	4	9	0	30	12	Slow	
2	11	0	11	4	8	4	Immediate	
4	10	6	10	10	15	4	Slow	
2	8	13	9	4	8	7	Immediate	Clysis
4	10	5	10	11	8	6	Slow	Intravenous
4	6	12	7	15	12	1	Rapid	
4	8	3	8	8	17	5	Rapid	Intravenous
4	6	6	6	5	11	-1	Slow	Clysis
2	6	12	7	2	8	6	Immediate	Intravenous
3	7	7	7	0	8	-7	Rapid	Clysis
4	10	7	11	15	20	1	Rapid	Intravenous
2	7	9	8	0	9	7	Immediate	
2	15	4	14	14	5	-6	Immediate	
2	10	1	10	15	10	15	Immediate	Clysis
4	10	9	10	5	12	-4	Immediate	
3	12	0	11	4	20	-10	Rapid	
Failure	-	-	-	-	-	-	Failure	Intravenous
4	5	5	5	14	13	9	Slow	Clysis
3	5	4	5	4	8	0	Rapid	Clysis
3	13	3	13	0	9	-3	Rapid	Intravenous
2	18	10	18	10	8	0	Immediate	Intravenous
2	20	9	21	8	6	15	Immediate	Intravenous
4	5	10	6	1	11	7	Rapid	Intravenous
2	6	11	6	11	9	0	Immediate	Clysis
3	17	8	21	8	6	4	Rapid	Intravenous
3	7	7	8	3	16	12	Rapid	

CONCLUSIONS

Initial and limited experience with carob flour ("Arobon") in the treatment of acute diarrheal disturbances in infants has been encouraging. Disappearance of diarrheal stools appears to be hastened, thus permitting early re-alimentation and hydration by the oral route. Further clinical trial and comparison with other hygroscopic agents is indicated.

REFERENCES

- Moro, E.: Experimentelle Beiträge zur Frage der künstlichen Sauglingsernährung, München med. Wehnschr. 44: 2223, 1907.
- von Noorden, C., and Salomon, H.: Handbuch der Ernährungslehre: Enzyklopädie der klinischen Medicin, Allgemeiner Teil 5, Berlin, 1920, J. Springer Co., p. 601.
- Haas, Sidney V.: The Value of the Banana in the Treatment of Celiac Disease, Am. J. Dis. Child. 28: 421, 1924.
- Panconi, G.: Der Intestinale Infantilismus (Coeliakie): Weitere Erfahrungen mit der Frucht-Gemüse-Diat, Klin. Wehnschr. 9: 553, 1920.
- Birnberg, T. L.: Raw Apple Diet in the Treatment of Diarrheal Conditions in Children, Am. J. Dis. Child. 45: 18, 1933.

6. Catel, W.: Die Behandlung diarrhoischer Zustände im Klinidesalter mit Rohfruchtkuren, Forts. der Therap. 9: 329, 1933.
7. Baumann, T., and Forschner-Boke, H.: Untersuchungen zur therapeutischen Wirkungsweise von Apfel und Bananen Diat, Zeitschr. für Kinderhk. 56: 514, 1934. Reported in: J. A. M. A. 103: 1818, 1934.
8. Baumann, T.: Zur Wirkungsweise der Apfel und Bananen Diat in Sauglingsalter, Therapie der Gegenwart 77: 37, 1936.
9. Schmidt, H. A.: Die Aplonadiat bei Ernährungsstörungen im Sauglingsalter, Kinderarztl. Praxis 4: 221, 1933.
10. Wolff, S.: Die Morosche Apfeldiat zur Behandlung diarrhoischer Zustände, Deutsche med. Wehnsehr. 56: 2211, 1931.
11. Joslin, C. L.: Banana Therapy in Diarrheal Diseases in Infants and Children: A Preliminary Report, South. M. J. 29: 1007, 1936.
12. Megevand, J., and Riederer, V. de: Une nouvelle thérapeutique pour les troubles digestifs graves des nourrissons (dyspex), Rev. med. de la Suisse Rom. 61: 330, 1941.
13. Ramos, R., and Rozalen, M.: Un Nuevo Alimento-Medicamento: La Harina de Algarroba, Rev. Espan. de Farm. y Terap. 21: 1339, 1941.
14. Neyroud, M.: Carob Flour, a New Antidiarrheic Medicine, Ann. Paediat. 166: 113, 1946.
15. Martin du Pan, R.: The Antidyspeptic Properties of Ceratonia Siliqua, Ann. Paediat. 165: 205, 1945; The Carob Bean, Its Antidyspeptic Properties, Schweiz. med. Wehnsehr. 75: 763, 1945.
16. Butler, A. M., and Talbot, N. B.: Parenteral Fluid Therapy in Diarrheal Diseases, Am. J. Dis. Child. 72: 481, 1946.

FEBRILE CONVULSIONS IN CHILDHOOD: THEIR RELATIONSHIP TO ADULT EPILEPSY

MARGARET A. LENNOX, M.D.
NEW HAVEN, CONN.

THE significance of febrile convulsions is a matter of dispute, with opinion divided as to their significance and relationship to adult epilepsy. Husler¹ states that febrile convulsions bear no relationship to epilepsy. Faerber² believes that in some patients febrile convulsions are indistinguishable from epilepsy.

Thom³ and Patrick and Levy⁴ differ as to the exact amount by which an individual's chances of developing epilepsy are increased by infantile convulsions. They agree, however, that "it seems evident that infantile convulsions do tend to increase materially the risk of epilepsy and mental deficiency in later life."⁵ Both state that febrile convulsions are of less serious import than convulsions assigned to trauma or for which no cause can be found. Livingston, Bridge, and Kadji⁶ report seventy-six cases in patients whose first convolution was attributed to fever and who have been followed fifteen years. Sixty of these patients developed recurrent convulsions without fever. In a previous study⁶ we suggested that febrile convulsions appear to differ from epilepsy in degree rather than in kind. Since severity in epilepsy can be expressed only in terms of the number of spells (for any one type of spell) it is clear that, if our conception is correct, febrile convulsions represent an extremely mild form of the disease.

Whatever one's formulation as to the fundamental significance of febrile convulsions, it is possible for all observers to agree that the majority of children with febrile convulsions will have no further seizures during the rest of their life. Agreement can also be assured that a certain number of children with febrile convulsions will have adult epilepsy. Estimates as to the percentage of children who will be affected vary from 5 to 10 per cent. The percentage is probably of less practical importance than the determination of prognostic guides; it is of practical importance to have some clues as to which children may develop epilepsy and why, so that this outcome may be prevented if possible. Patrick and Levy⁴ emphasize the serious prognostic import of severe or focal convulsions. The free periods reported by them are interesting: in 40 per cent the interval was ten years or longer. These results contradict the contention of Livingston and associates⁶ that convulsions without fever do not occur at all if they have not started by the time the child is 5 or 6 years old, i.e., the first five years indicate the prognosis. In a previous study⁶ we found age at onset, sex, and family history to be of prog-

From the Department of Psychiatry and Mental Hygiene, Yale University School of Medicine.

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nostic importance, but agreed with Patrick and Levy¹ that the severity of the convulsion is by far the most important feature in the history. We have also found that the electroencephalogram has definite prognostic significance.⁷

Aside from the importance of febrile convulsions with respect to the development of epilepsy, febrile convulsions may cause brain pathology as evidenced by transient or permanent neurological deficit. Fever alone can cause brain pathology,⁸ as can convulsions.⁹ The combination of fever and convulsions is more damaging than either fever or convulsions alone.¹⁰ This susceptibility to brain pathology as a result of fever and/or convulsions characterizes infants almost exclusively and is not apparently related to the special susceptibility of infants to convulsions.¹⁰

We have extended our previously reported series of epileptics whose first convulsion occurred with fever. The early histories of these patients have been investigated and compared with the histories of children with febrile convulsions (most presumably benign) in an attempt to determine which clinical features suggest that further convulsions will develop.

METHOD AND MATERIALS

The subjects consist of children and adults referred to the Electroencephalography Laboratory because of recurrent seizures. If the first convulsion was attributable to fever and if the history was sufficiently detailed and accurate, the case was included in this study. Most cases were referred with such brief histories that we could not include them. For the most part, those included are patients admitted to the in-patient service whose histories are available, and patients referred to seizure clinic. Twelve of the seventy-seven patients referred for electroencephalography because of febrile convulsions later developed recurrent seizures without fever.

The histories were reviewed in order to obtain the following information: sex; age at onset; number of febrile convulsive episodes; severity of convulsions (for the purpose of this study, a convulsion was classified as severe if it lasted an hour or more, or if it started in or involved only one limb or one side of the body); family history of convulsions; height, duration and cause of fever; mental retardation (children were classified as retarded if the I.Q. was below 80 or if there was marked clinical evidence of developmental retardation); and birth history (classified as abnormal were breech deliveries, placenta previa with severe bleeding, high or middle forceps, cesarean delivery, twin birth, prematurity if the birth weight was less than 5 pounds, and hemorrhagic disease of the newborn infant).

The histories of these epileptic patients were compared with histories, similarly obtained, of 240 children with febrile convulsions, most of them presumably benign.

The electroencephalograms were obtained with four, six, and eight-channel Grass ink-writing electroencephalographs. Electrodes were placed on the frontal, central, parieto-occipital and temporal areas on both sides and were rerecorded with reference to interconnected, grounded ear leads and, in many instances, scalp-to-scalp and scalp-to-alternate-ear recordings were ob-

tained as well. Controls consisted of 373 normal unscreened children whose electroencephalograms were obtained in the Pediatric Clinic of the Grace-New Haven Community Hospital with the collaboration of Dr. Donal L. Dunphy, and at the Boston Children's Hospital. The latter records were made available to us through the courtesy of Dr. F. A. Gibbs and Mrs. E. L. Gibbs. In addition, we relied on the descriptions of normal electroencephalograms in the Gibbs' *Atlas of Electroencephalography*¹¹ and in the monograph by C. E. Henry.¹²

Electroencephalograms were classified according to the classificatory system of Gibbs, Gibbs, and Lennox.¹³ Records showing extreme slowing, with a predominance of high-voltage, rolling, one to three per second waves, were classified separately. Originally records in which slow waves appeared predominantly or exclusively in the occipital leads were classified separately, but we are now forced to the conclusion that these electroencephalograms are normal, and we have included them in the normal group.

RESULTS

The group of seventy-seven epileptic patients whose first convolution was attributable to fever in every case ranged in age from less than one year to 45 years. One-half the patients were 5 years old or younger. The time interval from the last febrile convolution to the first nonfebrile convolution varied from a few months to twenty-five years; in the majority it was within the first year. All types of convulsions occurred. More than one-half were grand mal, and one-third of the patients had symptoms indicating focal onset of the convulsions. Seven were classified as petit mal and six as psychomotor.

The electroencephalograms of the patients in this group were varied. Approximately one-third were normal, one-third paroxysmal, one-sixth focal, and the rest nonspecifically abnormal, i.e., fast or slow.

Prognostic features which appeared to be of importance concerned age at onset, sex, number of febrile convulsive episodes, and family history (Table I). By far the most important item in the history, however, was the severity of the convolution.

As compared with children with presumably benign febrile convulsions, patients whose febrile convulsions presaged epilepsy had an earlier age at onset (before one year in one-third), with more than three convulsions in a higher percentage of cases, and a higher percentage of epilepsy (as opposed to infantile or isolated convulsions) in the family history. Whereas boys outnumber girls in the febrile convulsive group by two to one, girls outnumber boys slightly in the epileptic group. Presumably this is due to the inclusion in this group of patients with petit mal epilepsy, which is more common in girls. Whatever the reason, it is apparent that the risk of developing epilepsy is greater for girls than for boys.

By far the most important prognostic feature is the severity of the convolution. A severe convolution with fever occurred in 61 per cent of epileptic patients, whereas it occurred in 40 per cent of "benign" febrile convulsions.

TABLE I. CLINICAL CHARACTERISTICS OF CHILDREN WITH FEBRILE CONVULSIONS AND OF CHILDREN WHOSE FIRST CONVULSIONS OCCURRED WITH FEVER BUT WHO LATER DEVELOPED RECURRENT SEIZURES WITHOUT FEVER

CLINICAL DATA	FEBRILE CONVULSIONS		EPILEPSY (FIRST CONVULSION FEBRILE)	
	NO. PATIENTS	%	NO. PATIENTS	%
Number	240	—	77	
Sex: male	149	62.1	36	46.8
female	91	37.9	41	53.2
Age at onset	236	—	75	—
1 year	54	22.9	25	33.4
1-2 years	149	63.2	40	53.4
3-4 years	23	9.7	8	10.7
5-7 years	10	4.2	2	2.5
No. febrile convulsive episodes	230	—	76	—
One or two	197	82.0	47	62.0
Three or more	43	18.0	29	38.0
Severity of febrile convulsions	176	—	53	—
Mild	106	60.2	20	37.6
Severe	70	39.8	33	62.3
Mental development	162	—	68	—
Normal	127	78.4	53	78.0
Abnormal	35	21.6	15	22.0
Birth History	187	—	66	—
Normal	136	72.8	49	74.3
Abnormal	51	27.2	17	25.8
Family history	199	—	66	—
None	109	54.8	41	62.1
Convulsions	90	45.2	25	37.9
(Epilepsy)	14	7.0	9	13.6
(Rare convulsions)	76	38.2	16	24.3
Both sides	11	5.5	4	6.2

Severe convulsions were more than twice as common under 3 years of age than at ages of 3 years and over.

There was no difference between the two groups with reference to cause of fever. The height of the fever tended to be somewhat lower in the epileptic group, since one-half had a convolution with a recorded temperature of 102° or less. Duration of fever was not known in enough patients to allow any conclusions to be drawn. There was no difference in birth history between the two groups, but if one considers only children under 5 (in whom the birth history is most likely to be accurate) 38 per cent had an abnormal birth history in the epileptic group as opposed to 27 per cent in the "benign" group. This supports the observation that an abnormal birth, even though no clinical symptoms are observed at the time, tends to increase the hazard of epilepsy.

The electroencephalogram appears to have definite prognostic value. Even in an inadequate three-year follow-up period, it has been possible to show a correlation between the electroencephalogram (taken within a week of the febrile convulsive episode) and the development of nonfebrile convulsions. Of patients with a normal electroencephalogram, 5 per cent have developed

convulsions without fever. By contrast, 17 per cent of patients with a moderately slow electroencephalogram, 25 per cent of patients with a paroxysmal electroencephalogram, 33 per cent of patients with an extremely slow or focal electroencephalogram, and 50 per cent of patients with an abnormally fast electroencephalogram have developed convulsions without fever. The figures cannot be thought of as definitive, but it is evident that an electroencephalogram is as important as a careful history in judging prognosis. Mistakes will occur in both directions: some children in whom every sign points to the "benignity" of the febrile convulsions will develop epilepsy. Some who have all the cards stacked against them will escape. In general, however, the clinical history and the electroencephalogram afford an indication as to the chances that epilepsy will develop.

Case histories which illustrate the predictability and unpredictability of the outcome follow:

CASE 1.—E. K., a 31-year-old unmarried white woman, was seen because of grand mal and psychomotor seizures which started at the age of 17 years. Past history revealed that at the age of 4 months she had a convulsion lasting three hours, attributed to fever, and caused by a respiratory infection. She was then entirely well until the age of 5 years, when she developed "feelings" which occurred several times a day in the summertime only and lasted until she was 10 years of age. She is completely unable to describe these feelings, but can only say that things looked strange to her. The "feelings" lasted a few minutes at a time and were not accompanied by loss of consciousness. She was again symptom-free until the age of 17 years, when monthly grand mal and more frequent psychomotor seizures commenced. The psychomotor seizures occur as often as fifteen a day and the longest free interval has been eight months; during the seizures the patient first has her aura of an indescribable "feeling." She then loses consciousness, stiffens, turns blue about the lips, and swallows repeatedly.

Birth was normal. There was no head injury or severe illness other than the one at 4 months of age. Family history is negative for convulsions.

The electroencephalogram shows paroxysmal slow waves.

Comment.—A prolonged febrile convolution at the susceptible age of 4 months apparently caused the pathology responsible for the patient's later focal, psychomotor, and generalized motor convulsions. In this case there was no family history of convulsions, so the attacks are assumed to be "acquired." The long free period between the patient's initial insult and first focal seizure symptoms is interesting, as is the long remission between these focal symptoms and the development of major attacks. The potential seriousness of a febrile convolution in a child under one year of age is evident from this case.

CASE 2.—D. G., a girl aged 14 years, was seen because of psychomotor seizures which started at the age of 7 years. She was born by breech delivery. At the age of 2 years, with a temperature to 104.5° F. due to pneumonia, she had repeated convulsions for seven hours. She recovered uneventfully and had no more seizure symptoms until the age of 7 years, when she developed psychomotor seizures. These seizures last as long as fifteen minutes, during which she is out of contact. She usually remains motionless, often leaning her head on her hand, but may continue activities inaccurately or do things she would

not ordinarily do, such as stepping out of a moving car. All of these spells are preceded by a peculiar feeling which the patient finds it impossible to describe. Sometimes there is only partial loss of consciousness when she "hears voices far away as if in a dream. . . . The words don't make sense."

Family history is negative for convulsions.

Electroencephalogram reveals two to three per second waves in the contralateral temporal lead on recording to alternate ears. On medication the electroencephalogram is normal.

Comment.—In view of the negative family history, the patient's seizures are assumed to be primarily acquired. Although the breech delivery may have contributed to the brain pathology, prime responsibility is assigned to the seven-hour febrile convulsion which the patient experienced at the age of 2 years. Clinical and electroencephalographic findings point to the temporal lobe as the site of origin of the epileptic disturbance and presumably as the site of the brain pathology.

CASE 3.—A. B., a girl, was seen at the age of 12 years because of petit mal spells which started at the age of 10 years. Past history revealed that the patient had five brief convulsions with fever, the first at the age of 8 months and the last at 5 years. The family history was positive in that the father had convulsions until the age of 12 years, and a brother had one brief convolution at the age of 3 years at the onset of fever due to pneumonia. Past history and birth history were normal. Electroencephalogram was diagnostic of petit mal epilepsy.

Comment.—In this patient the positive family history suggests that the epilepsy is primarily "genetic" and that the febrile convulsions were the first evidence of epilepsy. The only historical item suggestive that secondary factors may have played some role in the development of epilepsy is the fact that the first convolution occurred when the patient was not yet one year old, a time when brain pathology is most readily produced.

CASE 4.—G. M., a female child, was referred for electroencephalography at the age of 2 years, 3 months. She was born after a long labor but there was no apparent injury and development was normal. Family history was positive in that the mother had many convulsions in a two-week period in infancy, but recovered uneventfully and had no subsequent convulsions.

At the age of 10 months the patient had a convolution lasting a few minutes with a temperature to 103° F. At 11 months she had repeated right-sided convulsions for twenty-four hours. Temperature reached 107° F. during the first day, and some elevation lasted four days. When she was first seen two months after the acute episode, she had a right spastic hemiparesis, a right homonymous hemianopsia, and a left-sided electroencephalographic focus. Eighteen months later her physical and electroencephalographic findings had not changed, but she had had no further convulsions.

Comment.—All features in this case, the difficult birth, occurrence of prolonged convulsions with high fever at less than one year of age, electroencephalographic and physical evidence of brain damage, and positive family history, suggest the likelihood that epilepsy will develop, yet this has not as yet happened. Admittedly the eighteen-month follow-up period is far too short.

CASE 5.—R. G., a male child aged 2 years, 10 months, was admitted to the New Haven Hospital because of one ten-minute grand mal convulsion. This occurred with a temperature of 104° F. caused by pneumonia. Temperature subsided in three days. A waking and sleeping electroencephalogram was obtained six days after the acute episode and was normal. Past history was unrevealing except that the patient had measles at the age of 2 years. Birth and development were normal. Family history was negative for convulsions.

The patient did not return to the hospital, but a nurse made a home visit three years after the initial episode. At this time the patient was six and had been entirely well until six months previously when recurrent convulsions without fever developed.

Comment.—Age at onset, brief convulsion, negative family, birth, and developmental history, and normal electroencephalogram all suggested that the patient's one febrile convulsion was benign. Yet recurrent convulsions without fever started at the age of 6 years.

DISCUSSION

Interest attaches to febrile convulsions because of their frequency, their unexplained clinical characteristics, their short-term sequelae, and their relationship to adult epilepsy.

Convulsions in children under 5 years of age are surprisingly frequent; they occur in 5 per cent³ to 7 per cent⁴ of the normal population, and are attributable to fever in one-half of the cases.

The clinical features of febrile convulsions are well known; in two-thirds of the cases they occur in boys between the ages of one and 3 years with a rapid elevation to a temperature of 103° F. or more. The fever is usually attributable to respiratory infection and is usually of short (one-two days') duration.⁷ Although Patrick and Levy⁴ state that all "benign" febrile convulsions are mild, severe convulsions occurred in 40 per cent of our presumably "benign" cases.⁷ The family history is positive for convulsions, usually infantile, in 45 per cent of our cases, and in 3 per cent of children who do not have convulsions with fever.⁴ These facts are well known, yet no explanation for the peculiar susceptibility to febrile convulsions is known to us.

Although fever is most often complicated by convulsions at the ages of one and 2 years, it is most likely to produce brain pathology in young infants under the age of one year.¹⁰ This is another peculiar age susceptibility for which there is no apparent explanation. When convulsions complicate the fever, the hazard of brain pathology is greatly increased, and this is especially so if the convulsions are severe or the fever prolonged.¹⁰ Severe convulsions occurred twice as often under 3 years as over that age in this series. It is thus apparent that children under 3 years with febrile convulsions run a greater risk of brain pathology than do children with fever or febrile convulsions over 3 years old. Sometimes the only evidence for brain pathology is an extremely slow electroencephalogram in the first week after the acute episode, sometimes prolonged coma or drowsiness, sometimes transient or permanent neurological

findings, or mental retardation. Sometimes the only evidence of brain trauma inflicted by the febrile convolution is the development, after months or years, of seizures often of focal onset or nature. Cases 1 and 2 are examples of this.

For brain pathology incurred as the result of the combined effect of fever and convulsions is one of the prime factors predisposing to the development of recurrent seizures or epilepsy. This accounts for the clinical finding that the occurrence of febrile convulsions before the age of one year, and the occurrence of severe convulsions both carry relatively serious import for the development of recurrent nonfebrile convulsions. This also accounts for the relatively serious import of extremely slow and focal electroencephalographic abnormalities within a week of the convolution. Brain damage attributable to birth injury also increases the likelihood that epilepsy will develop, especially if it is evidenced by an abnormally fast electroencephalogram.⁷

In other instances the epilepsy appears to be genetically determined, and in these cases, as in Case 3, one agrees with Faerber² that the febrile convulsions were the first evidence of epilepsy.

Most often there are evidences that both genetic and acquired, often multiple acquired factors are jointly responsible for the development of epilepsy. "It is the purpose of this article . . . to point out that *in a single individual* (with seizures) the etiological factors are usually multiple."¹⁴

The prevention of brain pathology and the prevention of epilepsy are aspects of the same problem, and require the prevention of prolonged fever in infants under one year of age and of severe febrile convulsions in infants under 3 years of age. If a child has had a febrile convolution, reliance cannot be placed on aspirin and phenobarbital in the event of a fever to avoid further convulsions, since the convolution is often the first evidence of the fever. It is more effective to give regular anticonvulsant medication to children under 3 years of age after the first febrile convolution, and to make a vigorous effort to shorten a convolution, when it occurs, as well as its precipitating fever. The prevention of brain pathology also depends on the prevention of anoxemia⁸ and of dehydration¹⁰ insofar as is possible.

In conclusion, with reference to the significance of febrile convulsions, subsequent experience has not caused us to change the opinion expressed three years ago. "We do not wish to deny what is well known—that the great majority of children with febrile convulsions will have no further seizures during the rest of their life. We do wish to emphasize the many interconnections between 'epilepsy' and febrile convulsions. We have been struck by the prominent hereditary factor demonstrated in febrile convulsions, and the relative frequency with which children with febrile convulsions develop recurrent seizures as compared with the 'normal' population. If one defines epilepsy as a disease characterized by recurrent seizures, one must certainly exclude from this category the majority of children with febrile convulsions. If one applies the broader and possibly more accurate definition of epilepsy as 'hereditarily determined convulsions,' then febrile convulsions would certainly be classed as 'epilepsy.' According to this conception, febrile convulsions differ from epilepsy as a disease only with respect to severity, but there

is no real difference in kind. This formulation appears to fit the facts better than the assumption that epilepsy and febrile convulsions are two distinct disease entities and have nothing to do with each other."¹⁶ To the objection "but we can't call febrile convulsions epilepsy, for if we do, then some of our best people have epilepsy" we can only assent that some of our best people do, indeed, have epilepsy.

SUMMARY AND CONCLUSIONS

1. Clinical histories of patients with febrile convulsions are compared with the histories of patients with epilepsy whose first convulsions were febrile.
2. Unfavorable prognostic features, suggesting the likelihood that recurrent seizures may develop, are: an early age at onset (under one year); prolonged or focal convulsions; an abnormal birth history; a history of many febrile convulsive episodes; a family history of epilepsy; an abnormal electroencephalogram; and female sex. Most often several of these factors in combination appear to be responsible for the development of epilepsy.
3. The prevention of epilepsy requires the prevention of prolonged fever in children under the age of one year and of prolonged or focal convulsions in children under the age of 3 years.

REFERENCES

1. Husler, J.: *Ergeb. der inn. Med. und Kinderh.* 19: 624-738, 1921.
2. Faerber, E.: *Klinische Beobachtungen über die initial Krämpfe im Kindesalter*, Jahrb. f. Kinderh. 124: 148-58, 1929.
3. Thom, D. A.: Convulsions of Early Life and Their Relation to the Chronic Convulsive Disorders and Mental Defect, *Am. J. Psychiat.* 98: 574, 1942.
4. Patrick, H. T., and Levy, D. M.: Early Convulsions in Epileptics and in Others, *J. A. M. A.* 82: 375, 1924.
5. Livingston, S., Bridge, E. M., and Kadji, L.: Febrile Convulsions, Clinical Study With Special Reference to Heredity and Prognosis, *J. PEDIAT.* 31: 509-512, 1947.
6. Lennox, M. A.: Febrile Convulsions in Childhood, *Proc. Assn. Res. Nerv. Ment. Dis.* 26: 342-65, 1946.
7. Lennox, M. A.: Febrile Convulsions in Childhood, *Am. J. Dis. Child.*, in press.
8. Hartman, F. W.: Lesions of the Brain Following Fever Therapy, *J. A. M. A.* 109: 2116-20, 1937.
9. Zimmerman, H. M.: The Histopathology of Convulsive Disorders in Children, *J. PEDIAT.* 13: 859, 1938.
10. Unpublished observations.
11. Gibbs, F. A., and Gibbs, E. L.: *Atlas of Electroencephalography*, Cambridge, Mass., 1941, Lew Cummings Co.
12. Henry, C. E.: *Electroencephalograms of Normal Children*, Monographs Soc. Res. Child. Dev. 9: 1944.
13. Gibbs, F. A., Gibbs, E. L., and Lennox, W. G.: Electroencephalographic Classification of Epileptic Patients and Control Subjects, *Arch. Neurol. & Psychiat.* 50: 111, 1943.
14. Lennox, W. G.: The Multiple Causes of Seizures in the Individual Epileptic Patient, *New England J. Med.* 209: 386-9, 1933.

EVALUATION OF THE COOMBS TEST IN CONGENITAL HEMOLYTIC DISEASE OF THE NEWBORN INFANT

ISADORE ROTHSTEIN, M.D., AND CHARLES T. FRIED, M.D.
NEW YORK, N. Y.

IN 1945 Coombs, Mourant, and Race¹ described a new method for the detection of Rh antibodies by the use of a serum prepared from rabbits immunized with human serum or its globulin fraction. This serum is used to demonstrate the presence of a form of Rh antibody which apparently is adsorbed on the surface of erythrocytes. When the test is positive, visible clumping of the affected red blood cells occurs, and this reaction has been referred to as the Coombs test or developing test.² The test is of considerable practical value in congenital hemolytic disease of the newborn infant, or erythroblastosis fetalis, in which condition it has been used to detect a type of maternal Rh antibody and to examine the erythrocytes of the newborn infant for adsorbed antibodies. The test is not specific for Rh antibodies as it is also positive in cases of acquired hemolytic anemia not due to Rh sensitization.³ The purpose of this paper is to indicate the value of the Coombs (developing) test in the diagnosis and management of congenital hemolytic disease of the newborn infant.

Since 1948 several hundred Coombs tests have been performed in the laboratory of this hospital on the blood of newborn infants in order to rule out congenital hemolytic disease of the newborn infant. The usual indications for the performance of the test were (1) early onset of jaundice in a newborn infant, (2) infants born of Rh negative mothers in whom there may or may not have been a previous examination for Rh antibodies and (3) cases of congenital hemolytic disease and related conditions requiring differential diagnosis. Twenty cases have been selected from this latter group as illustrative of the value of the Coombs test as an aid in the diagnosis and management of congenital hemolytic disease. (See Table I.)

Case 1, Death of Erythroblastotic Infant Prior to Use of Exchange Transfusions.—This Rh-positive infant was born jaundiced of an Rh-negative mother. The Rh antibody status of the mother was not known at the time of delivery but was later found to be positive for blocking antibodies in a titer of 1:16. The jaundice was progressive and marked. At no time was there any appreciable anemia or erythroblastemia. Therefore, simple transfusions were withheld. On the fourth day of life the jaundice was deeper and convulsions occurred. Blood was sent elsewhere for a Coombs test which was reported as 4 plus a few hours before death. The necropsy showed kernicterus. This case exemplifies

From the Department of Pathology and the Department of Pediatrics, The Bronx Hospital, New York, N. Y.

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the importance of performing the Coombs test immediately upon the birth of every jaundiced infant.

Cases 2, 3, 4, 5, 6, and 7, Exchange Transfusion Group.—These infants all showed 3 to 4 plus Coombs reactions and were given exchange transfusions within a few hours of the time of birth. One infant died forty-eight hours later, from either cardiac failure or kernicterus. Permission for necropsy was not granted. All of the remaining infants were well six months to one year later with no sequelae. However, a much longer follow-up period is advisable for adequate appraisal of results from the standpoint of possible mental or neurological disturbances. The mothers showed marked variability in their Rh sensitization. The mother in Case 7 showed no agglutinating or blocking antibodies but 2 plus "cryptagglutinoids"¹³ were found in her blood with the aid of Coombs serum. The presence of strongly sensitized red blood cells in any newborn infant as demonstrated by a 3 to 4 plus Coombs test performed at birth was considered an immediate indication for an exchange transfusion regardless of the presence or absence of clinical symptoms. Exchange transfusions were done as soon after birth as arrangements could be made, usually within the first few hours. In three of the cases a Coombs test was done on the day following the transfusion and showed a reversal to negative in each instance, indicating fairly complete removal of sensitized red blood cells. Two infants required additional small simple transfusions to overcome the anemia due to continued hemolysis of the remaining sensitized erythrocytes which replacement transfusion failed to remove.

Cases 8, 9, 10, 11, and 12, Group in Which Exchange Transfusion Was Not Performed.—Cases 8, 9, and 10 were similar in that jaundice was noted within twenty-four hours of birth and the Coombs test was negative. The impression was early icterus neonatorum rather than mild hemolytic disease. Case 11 developed slight jaundice at 24 hours but no anemia or erythroblastemia. Because of the 2 plus Coombs test, it was felt that this child could be followed expectantly. The infant recovered without specific treatment. Case 12 showed slight jaundice at 6 to 12 hours but no anemia or erythroblastemia. Inasmuch as the jaundice did not increase, exchange transfusion was not done although the child had a 3 plus Coombs test. Only one simple transfusion was needed to overcome a mild anemia which appeared later.

Cases 13, 14, 15, 16, and 17, Group With O-A-B Incompatibility.—A negative Coombs test was obtained in all of these infants. Treatment was conservative and recovery was the rule. Case 17 required no transfusions, whereas Case 15 was given more than one simple transfusion with group-specific A and B substances added. Four of the cases occurred in primigravida.

Cases 18, 19, and 20, Miscellaneous.—In the first two cases the Coombs test was of value in the differential diagnosis. Case 18 was an infant born jaundiced about the face, groin, and umbilical cord. Moderate anemia was present. The probable etiology was hemorrhage from premature separation of the placenta. Erythroblastosis was considered unlikely when the Coombs test was reported negative and there was no group or Rh incompatibility. Case 19¹⁴ showed icterus neonatorum on the fourth day and a routine blood count revealed 21 per cent

TABLE I*

MATERIAL												TREATMENT				REMARKS		
No.	GRW	IDV	PABA	TYPE	RH	ANTI RH	ANTI B	JAUN	DIGI	WBC	WBC	NOR	MUL	TYPN	RH	COOMBS	TRANSFUSION	REMARKS
1	III	II	AB	neg.	I	16	—	at birth	130	5.0	18,000	1/100	B	pos.	I plus	None	Died on fourth day with kernicterus	
2	II	I	AB	neg.	I	256	—	3 plus in 5 hours	60	2.26	14,700	36,000	—	—	I plus	Exchange transfusion	Died in 18 hours	
3	II	I	O	neg	I	8	—	3 plus in 12 hours	60	3.11	53,000	13,500	A	pos.	I plus	Exchange transfusion and 1 unit	Recovered	
4	III	II	neg.	I	I	—	1 plus	12 ^t	5.25	21,500	7,000	O	pos.	3 plus	Exchange transfusion	Recovered		
5	II	II	A	neg.	I	61	—	3 plus at birth	100	3.6	37,500	41,000	A	pos.	3 plus	Exchange transfusion	Recovered	
6	II	I	A	neg.	I	1,000	—	2 plus in 12 hours	84	3.9	24,000	1,600	O	pos.	3 plus	Exchange transfusion	Recovered	
7	VI	IV	A	neg.	cryoplag	—	1 plus in 3 hours	88	3.94	12,500	750	O	pos.	3 plus	Exchange transfusion and 2 transfusions	Recovered		
8	III	II	—	pos.	—	—	3 plus in 18 hours	132	5.5	11,000	13,600	A	pos.	neg.	None	Recovered without treatment		
9	II	I	—	—	—	—	1 plus in 10 hours	122	6.15	38,000	3,500	A	pos.	neg.	None	Recovered without treatment		
10	II	I	O	neg.	neg.	—	1 plus in 24 hours	130	4.8	21,000	2,500	—	neg.	neg.	None	Recovered without treatment		

11	II	0	neg.	1.8	—	1 plus in 24 hours	118	5.2	13,500	1,500	—	pos.	2 plus	None	Recovered without treatment				
12	II	1	0	neg.	1.8	—	1 plus in 6:12 hours	120	5.0	19,500	1,000	O	pos.	3 plus	1 trans- fusion	Recovered with one transfusion			
13	I	0	0	neg.	neg.	Anti-A	3 plus in 1:640	4.0	23,000	3,500	A	pos.	neg.	1 trans- fusion	Recovered with one transfusion				
14	I	0	0	CD†	—	Anti-A	1 plus in 1:320	108	3.9	36,000	11,900	A	CD†	neg.	1 trans- fusion	Recovered with one transfusion			
15	I	0	0	pos.	—	Anti-A	1 plus in 1:512	110	6.6	17,600	1/100	A	pos.	neg.	2 trans- fusions w. A&B subst.†	Recovered with two transfusions			
16	II	1	0	pos.	neg.	Anti-A	4 plus in 1:512	80	3.5	25,400	5,900	A	pos.	neg.	1 trans- fusion w. A&B subst.†	Recovered with one transfusion			
17	II	1	0	neg.	—	Anti-B	1 plus in 1:1024	104	4.2	23,000	12,000	B	pos.	neg.	None	Recovered without treatment			
18	I	0	0	pos.	—	—	2 plus at birth	80	3.9	32,000	3,500	O	pos.	neg.	None	Anemia due to premature sepa- ration of pla- centa			
19	II	0	0	pos.	neg.	—	Fourth day	140	6.5	11,500	3/100	O	pos.	neg.	None	21% myeloblasts. Leucemoid re- action			
20	II	1	0	pos.	neg.	—	none	118	5.1	16,800	none	O	pos.	neg.	None	Hemolytic anemia pregnancy; Baby not affected			

*A few omissions of pertinent data were due to circumstances beyond our control.

†Normal = normoblasts,

CD = Rh subtype,

A&B subst. = A and B group specific substances.

myeloblasts. Many additional blood counts all demonstrated a leucoeytosis with about the same number of primitive cells. By the third month, the infant's blood picture returned to normal and the episode was thought to be a leucemoid reaction. Hemolytic disease was excluded by a negative Coombs test on the infant, a negative Rh antibody titer in the mother, and no incompatibility of blood types. Case 20 is that of a normal infant delivered of a mother who had an acquired chronic hemolytic anemia of pregnancy. The mother's blood showed no Rh antibodies and no circulating hemolysins by the technique of Dameshek and Schwartz,⁵ but her washed erythrocytes showed 3 plus clumping with Coombs serum. The newborn infant was normal in every respect and the Coombs test was negative. The hemolytic disease in the mother disappeared soon after delivery. The positive Coombs test in the mother indicated that a hemolytic antibody of some kind existed in her blood. Apparently it had not been transmitted to the infant.

DISCUSSION

The primary objective for the effective management of congenital hemolytic disease of the newborn infant is to rid the involved infant of immunologically altered erythrocytes and circulating foreign antibody as soon as possible after birth. Immediate replacement or exchange transfusion serves these purposes. Whether exchange transfusion has any effect on antibody which is already fixed in tissue cells is still debatable. However, further tissue damage is minimized by early removal of foreign circulating antibody.

The problem in the past has, therefore, been the proper selection of cases of congenital hemolytic disease for exchange transfusion. The height of the mother's Rh antibody titer is not always correlated with the severity of the disease in the infant. This is shown by our series of cases. However, many infants are born with no evidence, either clinical or hematologic, of erythroblastosis, and develop signs of the disease rapidly after several hours or even days. In our limited experience, which is in agreement with that of others,⁶ the Coombs test is best correlated with the degree of the disease process in the Rh-sensitized infant. It has fulfilled the requirement for a rapid, simple, and reliable test which can be employed at birth on cord or infant's blood for the diagnosis of congenital hemolytic disease and for consideration of proper therapy.

Until more is known about the prevention of residua of erythroblastosis, it seems advisable to use exchange transfusions in borderline as well as in manifest cases. Some infants with strongly positive Coombs tests have recovered without such transfusions, as in Case 12, but the wisdom of this procedure cannot be estimated until there has been a long period of follow-up for sequelae.

The results of the Coombs test in erythroblastotic infants with O-A-B incompatibility bears emphasis. The test was negative in all of our cases, which is the opposite of what one finds in Rh sensitization. This fact has helped differentiate cases of suspected sensitization to both O-A-B and Rh factors.

None of our cases of *icterus neonatorum* gave a positive Coombs test. Even when there was a fall in hemoglobin to below 100 per cent in the newborn in-

fant this was regarded as an exaggeration of the normal neonatal processes of blood destruction and not hemolytic disease due to Rh incompatibility, provided that O-A-B incompatibility could be excluded.

CONCLUSIONS

1. In a series of twenty selected cases, the Coombs (developing) test has proved to be of great value in the diagnosis and management of congenital hemolytic disease of the newborn infant.

2. The results of the test appear to be more closely correlated with the severity of the disease in cases of Rh sensitization than any other finding.

3. The test is very helpful in the proper selection of cases for exchange transfusion.

REFERENCES

1. Coombs, R. R. A., Mourant, A. E., and Race, R. R.: A New Test for the Detection of Weak and "Incomplete" Rh Agglutinins, *Brit. J. Exper. Path.* 24: 255, 1945.
2. Hill, J. M., Haberman, S., and Jones, F.: Hemolytic Rh Immune Globulins: Evidence for a Possible Third Order of Antibodies Incapable of Agglutination or Blocking, in Hill, J. M., and Dameshek, William: The Rh Factor in the Clinie and the Laboratory, New York, 1948, Grune and Stratton, p. 80.
3. Boorman, K. E., Dodd, B. E., and Loutit, J. F.: Hemolytic Icterus (Acholuric Jaundice) Congenital and Acquired, *Lancet* I 250: 812, 1946.
4. In preparation.
5. Dameshek, W., and Schwartz, S. O.: The Presence of Hemolysins in Acute Hemolytic Anemia, *New England J. Med.* 218: 75, 1938.
6. Sturgeon, P.: Immuno-hematologic Observations on Erythroblastotic Infants, *Pediatrics* 3: 318, 1949.

THE TREATMENT OF PRURITUS FROM CHICKEN POX WITH PYRIBENZAMINE

LOUIS B. SILVERMAN, M.D.

GRAND FORKS, N. D.

AT A recent meeting several pediatricians expressed interest in our experience with the use of antihistaminies for the relief of itching in chicken pox. The following observation, therefore, may be of some value to those who treat children.

There was an increased incidence of chicken pox in this area during the past season. One of our first patients had very severe itching with the disease. The customary treatment with antipruritic lotion, Aspirin, and sedation gave no relief. It was not long before the mother called and insisted that "something be done." For want of anything better, treatment with Pyribenzamine in elixir^e was instituted. Twenty milligrams of Pyribenzamine were given four times daily. After two or three doses, the child obtained complete relief from itching. A week or so later, another patient with complaint of severe itching complicating chicken pox was given similar treatment and also experienced relief within a short time. Since that time Pyribenzamine has been routinely prescribed as part of the symptomatic treatment for every patient with chicken pox. Over a period of several months, with many new cases appearing every week, we do not recall any child complaining of itching with chicken pox since this type of medication was included. In addition, it seemed that the number of secondary skin infections was materially, if not entirely, reduced.

Although the relief obtained may have been entirely coincidental, it is our impression that the addition of the antihistaminic has been of value. It is doubtful whether the result was obtained by the sedative action which these drugs occasionally effect, since none of the children was especially drowsy. No attempt was made to use the antihistaminic in topical application. Keating and Code¹ have recently shown that the antihistaminic action of Pyribenzamine and other synthetic histamine antagonists is separate from, and not dependent on, their local anesthetic action. Whether chicken pox gives rise to some related histamine reaction in the skin is, of course, speculative, but the apparent relief from itching the Pyribenzamine offered in these patients might suggest this.

The average dose of Pyribenzamine approximated 2 mg. per pound of body weight in twenty-four hours. In the younger children the proprietary elixir was well tolerated. For older patients the 50 mg. tablets were more convenient. An amount sufficient to last the patient only three or four days was

From the Grand Forks Clinic.

*Tripeleannamine Hydrochloride, Pyribenzamine hydrochloride elixir, Ciba. Each 4 c.c. (approximately 1 teaspoonful) contains 20 mg. Pyribenzamine hydrochloride.

prescribed in each case. At times a combination of equal parts of Benadryl and Pyribenzamine was used.

No doubt many of the other antihistaminics would work as well. No patient with chicken pox suffered ill effects from the drug. It should be pointed out that the antihistaminic gave no relief to those patients who had painful ulcerated lesions of the oral or vaginal mucosa.

It may be of interest to note that Pyribenzamine gave relief to several children who had pruritis with the rash of measles. However, pruritus was not prevalent in our patients with measles, so that no appraisal could be made.

The antihistaminics have been used successfully for the relief of itching in a number of cases of dermatoses associated with pruritus. A review of recent literature indicates that the use of antihistaminics for the treatment of itching complicating chicken pox has not been reported. No doubt other physicians have offered antihistaminic preparations to patients with chicken pox and may have obtained the same results as reported here. It would be desirable to have this observation substantiated, if possible. All of our patients were treated in the home. Physicians who care for large groups of children in institutions are in the best position to make some type of control study when the opportunity arises.

Fortunately, chicken pox is usually not a serious disease. Nevertheless, in our experience, pustular dermatitis and cellulitis, though infrequent, have at times been dangerous complications. Secondary infections of the skin with *Staphylococcus aureus* and hemolytic streptococcus cause the most severe complications, and may be followed by acute glomerulonephritis. Stokes² writes that furuncles, impetigo, staphylococcal or streptococcal septicemia, abscesses, gangrene, and suppurative adenitis may occur as the result of scratching or lack of care in cleansing the skin of the hands. He states that scratching considerably increases the danger of these complications. Therefore, any useful addition to the symptomatic treatment for the relief of itching in chicken pox may help relegate this disease to an even more harmless status.

CONCLUSION

On the basis of recent clinical experience it is suggested that Pyribenzamine (and probably other antihistaminics) given orally, may offer prompt relief from the severe pruritus which often accompanies chicken pox.

Note: Since this paper was written, we have been informed that Pyribenzamine hydrochloride elixir has been replaced by Pyribenzamine citrate elixir, Ciba, 4 c.c. (approximately 1 teaspoonful) containing 30 mg. of Pyribenzamine citrate.

REFERENCES

1. Keating, J. N., and Code, C. F.: The Anesthetic and Antihistaminic Action of a Series of Antihistaminic Drugs in Human Skin, *J. Lab. & Clin. Med.* 33: 1609, 1948.
2. Stokes, Joseph, Jr., in Mitchell, A. G., and Nelson, W. E.: *Textbook of Pediatrics*, ed. 4, Philadelphia, 1945, W. B. Saunders Company, p. 453.

STUDIES ON THE CHEMOTHERAPY OF VIRUS INFECTIONS

II. FAILURE OF DARVISUL (PHENOSULFAZOLE) TO AFFECT THE COURSE OF EXPERIMENTAL AND CLINICAL POLIOMYELITIS

MORRIS SCHAEFFER, M.D.,* AND JOHN A. TOOMEY, M.D.
CLEVELAND, OHIO

INTRODUCTION

CONSIDERABLE interest was aroused by the announcement early in the summer of 1948 of a newly synthesized sulfonamide compound, Darvisul (phenosulfazole), which was purported to have remarkable prophylactic and therapeutic effects on poliomyelitis produced experimentally in mice. This was later officially reported by Sanders, Subba Row, and Alexander.¹ It was also claimed, although not published, that this drug was effective against human poliomyelitis as well.

The purpose of this communication is to report the failure of this drug in both experimental and clinical poliomyelitis. Since this paper was prepared other reports have been presented recently²⁻⁵ indicating similar negative results in experimentally infected mice but no other clinical trials have been reported to our knowledge.

METHODS

Drug.—The compound, Darvisul, or sodium phenosulfazole, was supplied in sterile ampules containing a 25 per cent solution for intravenous use and in 0.5 Gm. tablets for oral administration. Chemically it is somewhat related to the well-known sulfonamide drugs but differs in that it is a phenol rather than an aniline derivative. The structural formula was described to us as "N-(2 thiazoly) 1, 4, phenol sulfonamide." There is no satisfactory method for its determination in blood and body fluids. The Bratton and Marshall method applied to other drugs of the sulfonamide series cannot be utilized here.

Experimental.—Toxicity studies were conducted in mice and maximal, nonfatal doses were determined for mice, CFW strain weighing 10 to 15 Gm. The results of toxicity tests and antibacterial action as compared to that of sulfadiazine are given in Table I. The dosage schedule and treatment plan appears in Table II.

*The Department of Contagious Diseases, City Hospital, and the Department of Pediatrics, Western Reserve University, Cleveland, Ohio.

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^{*}Present address U. S. Public Health Service, Communicable Disease Center, Virus and Rickettsia Branch, R. t. 3, Box 436, Montgomery 7, Ala.

We wish to thank Dr. Benjamin Carey of the Lederle Laboratories Division of the American Cyanamid Company for making available to us prompt and generous supplies of the drug which we requested for this study.

TABLE I. BACTERIAL SENSITIVITY TO DARVISUL: TWENTY-FOUR-HOUR GROWTH

ORGANISM	MG. % DARVISUL REQUIRED TO INHIBIT GROWTH	
Staphylococcus	313	
E. coli	78	
Diphtheroid	156	
Proteus	625	
ACUTE 50 PER CENT TOXICITY (Test Animal: CFW Mice, 10 to 15 Gm.)		
	50% TOXIC DOSE	KILLING TIME
Darvisul	1.25 Gm./kilo	12 minutes
Sodium Sulfadiazine	2.60 Gm./kilo	6 hours

TABLE II. EVALUATION OF DARVISUL (PHENOSULFAZOLE) IN EXPERIMENTAL POLIOMYELITIS

TEST ANIMAL: CFW Mice, 10-15 Gm.

DARVISUL THERAPY: 25 m./mouse/day—I. P. in 4 divided doses until death or end of 30-day observation period

VIRUS: LANSING STRAIN: Dose, 1 Ld 50 intracerebrally

	NO. MICE IN GROUP	AVERAGE INCUBATION PERIOD IN DAYS	MOUSE WITH OBSERVED PARALYSIS	PARALYZED MICE SURVIVING	TOTAL NO. DEATHS	% MICE WITH OBSERVED PARALYSIS	% TOTAL NO. OF DEATHS
Mice begun on treatment five days prior to virus injection	45	10	27	0	38	60	84
Mice treated after virus injection	50	11	17	0	32	34	64
Untreated control mice	50	11	23	0	30	48	60

Virus.—A group of fifty mice were pretreated with the drug for several days, then inoculated with an Ld 50 dose of mouse-adapted Lansing strain poliomyelitis virus and treatment continued until an observation period of thirty days had elapsed.

A second group of fifty mice received treatment and virus simultaneously, while a third group served as untreated controls for comparison of infection rate and mortality. The results appear in Table III.

TABLE III. DRUG REACTIONS OF PATIENTS ON DARVISUL THERAPY

REACTION	NUMBER
Nausea and vomiting	10
Convulsions	
abortive	1
spinal	1
bulbar	2
Anorexia	1
Urinary retention	2 (?)
Rash	2
Total number of patients on Darvisul	68
Per cent experiencing reactions	26

Clinical.—Beginning in July, 1948, and for the duration of the season as cases of poliomyelitis were admitted to the hospital and the diagnosis established, they were separated into four categories: nonparalytic, spinal, corticobulbar, and respiratory. Each of these was listed and numbered consecutively on entry. The odd-numbered were treated and the even-numbered observed

as untreated controls for comparison. The treatment, following essentially the instructions given to us by Dr. Carey of the Lederle Laboratories, consisted of the administration of 0.4 Gm. per kilogram of body weight in glucose or saline by the intravenous route for the first two days, followed by oral administration of the same dose in tablet form for the next three days. Toxic effects of the drug were noted. Except for a larger number of patients with emesis, the reactions were more or less similar to those observed with other sulfonamides. The reactions are listed in Table III. Follow-up of patients of both the treated and control groups consisted of general evaluation, or frequent muscle examination regarding progression of paralysis, lack of change or improvement in the period immediately following institution of therapy and for several weeks to months afterward. The results are presented in Table IV.

TABLE IV. CLINICAL APPLICATION OF DARVISUL IN THE TREATMENT* OF POLIOMYELITIS

TYPE ON ADMISSION	NO.	IMPROVED	PROGRESSED	NO CHANGE	EXPIRED
<i>Treated</i>					
Nonparalytic	22	3	Spinal 6 Bulbar 1	12	(Bulbar) 1
Spinal	35	19	Bulbar	14	1
Respiratory	3	0	0	3	0
Corticobulbar	8	4	0	3	1
Total	68	26	7	33	3
Per cent		38	10	47	5
<i>Controls</i>					
Nonparalytic	26	2	Spinal 5 Respiratory 1	18	0
Spinal	31	18	Respiratory 1	12	0
Respiratory	2	0	0	0	(Bulbar) 2
Corticobulbar	10	4	0	4	2
Total	69	24	7	34	4
Per cent		35	10	49	6

*These patients received 0.4 Gm. Darvisul per day, per kilo of body weight, diluted in 5 per cent glucose by intravenous drip for the first two days, and 0.4 Gm. per day kilo of body weight by mouth for three successive days.

CONCLUSION

The data presented above indicate clearly that Darvisul (phenosulfazole), when administered to experimentally infected animals or patients acquiring the disease naturally, has no effect whatever on the course of the infection.

REFERENCES

1. Sanders, M., Subba Row, Y., and Alexander, R. C.: Texas Rep. Biol. & Med. 6: 385, 1948.
2. Lo Grippo, G. A., et al.: Proc. Soc. Exper. Biol. & Med. 70: 528, 1949.
3. Cox, H. R., et al.: Proc. Soc. Exper. Biol. & Med. 70: 530, 1949.
4. Weil, M. L., and Warren, J.: Proc. Soc. Exper. Biol. & Med. 70: 534, 1949.
5. Francis, T., and Brown, G. C.: Proc. Soc. Exper. Biol. & Med. 70: 535, 1949.

THE TREATMENT OF POLIOMYELITIS WITH PHENOSULFAZOLE

RICHARD L. WHELTON, M.D., ESTON R. CALDWELL, JR., M.D., MARK H. LEPPER,
M.D., LEWIS K. SWEET, M.D., AND HARRY F. DOWLING, M.D.
WASHINGTON, D. C.

DURING the course of a screening program for compounds with antiviral activity, a sulfonamide, N(2 thiozolyl) phenol sulfonamide, named phenosulfazole,² was found to be effective in protecting mice infected with a strain of mouse poliomyelitis virus.¹ It also exerted some inhibiting effect on the propagation of the virus in tissue culture, although no actual destruction of the virus was demonstrable in serum. Since the drug was found to be of low toxicity in animals, a therapeutic trial in acute poliomyelitis in humans was indicated.

When, in August, 1948, phenosulfazole was made available to us, we decided to treat alternate poliomyelitis patients with the drug. During the months of August through November, 1948, we observed sixty-six patients admitted to the Isolation Division of Gallinger Municipal Hospital who had been diagnosed as having acute poliomyelitis. The following criteria were employed for the diagnosis of acute poliomyelitis: (1) a characteristic history, and (2) the presence of muscular weakness and/or the presence of cells in the spinal fluid with a normal dextrose content and negative cultures. Patients admitted after having passed through the acute phase of the disease were not utilized in the present study.

If, on admission, a patient was considered suitable for study as far as diagnostic criteria and activity of the disease were concerned, he was placed in one of two groups by strict alternation without selection. One group received 75 mg. per kilogram of body weight every six hours for the first twenty-four hours, and for a longer period of time in patients with the bulbar form of the disease. This intravenous therapy, during the last twelve hours of the first twenty-four-hour period, was supplemented by phenosulfazole orally at the rate of 150 mg. per kilogram of body weight per day. Subsequent therapy was at the rate of 300 mg. per kilogram of body weight per day by mouth, and was continued until signs of activity had subsided for two to three days. The intravenous doses were prepared by dissolving 10 Gm. of phenosulfazole in 1 liter of isotonic sodium chloride or 5 per cent dextrose solution, using the volume required to obtain the desired dose.

The other group of patients received an intravenous injection of isotonic saline or 5 per cent glucose solution which had been colored with 100 to 200 mg. of Gantrosant per liter. The two intravenous solutions were indistinguish-

¹From the George Washington University Medical Division and the Infectious Disease Service, Gallinger Municipal Hospital, and the George Washington University School of Medicine.

²Supplied by the Lederle Laboratories Division of the American Cyanamid Company, Pearl River, N. Y. under the name of Divarsil.

³Supplied by Hoffman-LaRoche Inc., Nutley, N. J.; the chemical formula is 3,4-dimethyl-sulfanilamido-isoxazole.

able as to color. Oral placebo tablets were made of dextrose and these two placebos were administered on dosage schedules exactly the same as for phenosulfazole. In an attempt to make the study as objective as possible, two of the other investigators supplied the drug and thus controlled the alternation of cases. Evaluation of the response to therapy was carried out in each case by the investigators, who were not aware of which solution a particular patient had received, and also by the house and visiting staffs, who were not cognizant that a controlled experiment was being attempted.

RESULTS

Phenosulfazole was given to thirty-two patients, while thirty-four patients made up the control group. The patients have been classified according to the type of disease in Table I. Since this classification was made after discharge, it includes all patients who were admitted with, or subsequently developed, paralysis while under therapy, and is not a reliable guide as to the quality of the groups on admission.

TABLE I

CONTROL SERIES		PHENOSULFAZOLE SERIES	
No. patients	34	No. patients	32
<i>Classification</i>			
Bulbar spinal	3	Bulbar spinal	4
Bulbar	1	Bulbar	1
Spinal	9	Spinal	13
Nonparalytic	21	Nonparalytic	14

Certain clinical and laboratory data obtained on admission are given in Table II. This table emphasizes the similarity between the two groups of patients, in spite of the wide range of variation within the disease itself.

TABLE II. DATA OBTAINED ON ADMISSION IN PATIENTS TREATED WITH AND WITHOUT PHENOSULFAZOLE

	CONTROL SERIES	PHENOSULFAZONE SERIES
Age (years)		
Mean	16.0	16.0
Range	1-37	1-36
Duration of Illness Before Admission (days)		
Mean	3.7	3.5
Range	1-8	1-10
Initial Temperature (degrees F.)		
Mean	101.6°	101.5
Range	99-104.2°	98.8°-104°
<i>Initial Cerebrospinal Fluid Findings</i>		
Leukocyte count (per cu. mm.)	148	143.8
Mean	3-800	13 390
Range		
Polymorphonuclears (per cent)	35.0	40.0
Mean	6.92	0.90
Range		
Polymorphonuclears (absolute number)	89.2	76.0
Mean	2.0 632.0	0 255
Range		
Protein (mg. per 100 c.c.)	71	99.2
Mean	31-121	35-251
Range		

In an attempt to find criteria that would be useful in deciding the effectiveness of phenosulfazole, the following were selected: progression of, or development of, paralysis after the start of therapy, and the duration of fever over 101° F. There was one fatal case in each group. In the treated series, death occurred in a 25-year-old white female admitted on the fourth day of her illness. After the paralysis, which was of the Landry type, had spread rapidly, the patient died on the second hospital day. Death apparently was due to involvement of vital medullary centers. The patient in the control group who died was a 17-year-old white female. Death took place in a respirator on the eighth hospital day. Post-mortem examination revealed almost complete atelectasis of all lung tissue.

TABLE III

	CONTROL SERIES	PHENOSULFAZOLE SERIES
Paralysis present on admission	11	15
Progression after twelve hours of therapy	2	2
Progression after twenty-four hours of therapy	9 (5)*	16 (4)*
Deaths	1	1
Duration of fever over 101° F. (hr.)		
All cases		
Mean	27.9	48.8
Range	8-104	16-336
Uncomplicated cases		
Mean	26.1	28.3
Range	8-104	16-144
Duration of fever over 100° F. (hr.)		
All cases		
Mean	28.5	49.5
Range	8-116	16-336
Uncomplicated cases		
Mean	29.4	27.5
Range	8-116	16-144

*The figures in brackets represent cases in which muscle weakness was noted by the orthopedic or physiotherapy staff after the acute process had subsided.

The case record of each patient was evaluated as to the presence or absence of muscular weakness on admission. Further evaluation of the progression of muscular weakness was made at the end of twelve hours and again twenty-four hours after therapy had been instituted (Table III). It can be seen that progression was more frequent in the treated than in the untreated group, as determined by the house officers as well as by the final muscle check. As shown in Table III, the duration of fever for the entire experimental group was longer than for the entire control group, although when fever caused by obvious complicating bacterial infection is eliminated, the duration was practically identical for the two groups.

For the purpose of studying the toxic effects of phenosulfazole, we have included six patients who were treated by us at Gallinger Hospital and elsewhere, and who were not included in the investigational series. Among the entire group of seventy-two patients, no toxic effects from phenosulfazole were observed except mild nausea in some cases when the drug was being given intravenously. This could usually be controlled satisfactorily by decreasing the rate of flow. Four of seven patients who received a second course of the drug orally complained of slight nausea only.

SUMMARY AND CONCLUSION

1. Phenosulfazole was given to thirty-two patients with acute poliomyelitis in strict alternation with thirty-four patients who were observed as controls. The two groups were comparable with regard to the duration of the illness, the presence of paralysis, and the cerebrospinal fluid findings on admission.
2. There was no appreciable difference in the outcome in the two groups.
3. No toxic effects were observed in the patients treated with phenosulfazole.
4. It is concluded that phenosulfazole has no effect upon the clinical course of acute poliomyelitis.

REFERENCE

1. Sanders, M., SubbaRow, Y., and Alexander, R. C.: An Effective Antiviral Synthetic, Texas Rep. Biol. & Med. 6: 385, 1948.

SUBLUXATION OF THE ATLANTO-AXIAL JOINT: SEQUEL TO INFLAMMATORY PROCESSES OF THE NECK

ALBERT W. SULLIVAN, M.D.

ROCHESTER, N. Y.

INTRODUCTION

THE type of atlanto-axial subluxation associated with infections of the tissues of the neck occurs almost exclusively in children, yet has received little attention from pediatricians, who are usually first consulted when the condition occurs.

Experience with four children seen at The New York Hospital with this syndrome and a review of the literature have demonstrated that difficulty in making this diagnosis frequently delays treatment for many months or even years.¹ A particularly confusing factor is the roentgenogram, since routine views frequently do not reveal minor subluxations.^{1, 2} The selectivity of this condition for the pediatric age group, the paucity of reported cases in the pediatric literature, and recently developed techniques in diagnosis have prompted the present report.

CASE REPORTS

CASE 1.—M. J. G., a 6½-year-old white girl, was admitted to The New York Hospital in October, 1937, with the chief complaint of a stiff neck of four weeks' duration. Her family history was negative. She had had the usual childhood diseases and also removal of the tonsils and adenoids, but had otherwise been well.

Three weeks before admission she had rhinorrhea and a mild productive cough. Two weeks before admission she awoke with a painfully stiff neck which persisted despite hot gargles, heat, and massage prescribed by a private doctor. She was seen in the out-patient department here where a roentgenogram of the cervical spine showed an anterior subluxation of the atlas on the axis, and the child was admitted for treatment.

Physically she was a well-developed, well-nourished child. Her head was turned toward the left and was tilted toward the right shoulder; the chin was depressed forward. The head was held rigidly in this position; jarring or any motion of the neck was painful. There was tenderness of the left side of the neck and over the first (axial) spine. The pharynx was red and there were palpable anterior and posterior cervical lymph nodes. The neurological examination was negative.

Laboratory studies showed the urine to be negative and the white blood cell count to be 12,400 per cubic millimeter with a leucocyte differential count of 24 per cent lymphocytes, 4 per cent monocytes, 4 per cent eosinophiles, and 68 per cent polymorphonuclear cells.

The patient was placed in skeletal traction by means of a chin halter for fourteen days when x-ray examination showed reduction; a plaster neck jacket was then applied for forty-seven days. The end result was satisfactory functionally and cosmetically.

From The New York Hospital and the Department of Pediatrics, Cornell University Medical College, New York, N. Y.

CASE 2.—F. M., a 9-year-old white boy, was admitted to The New York Hospital in September, 1945, with the complaint of stiff neck for two months. His family history was unremarkable. He had had a right purulent otitis media at the age of 5 years and a tonsillectomy and adenoidectomy at the age of 7½ years.

Two months before admission, the patient received an injection of pertussis vaccine in the right arm, and within a few hours developed malaise, fever, and a moderate local reaction. The next day he awoke with a mild torticollis which became progressively worse and more painful until he could not walk without complaining of pain. No history of trauma or infection could be elicited. Three weeks before admission he was seen in the out-patient department of this hospital, where several diagnoses were considered, including myositis, radiculitis, meningitis, atypical poliomyelitis, tetanus, retropharyngeal abscess, cerebellar tumor, fracture, and dislocation. Roentgenograms of the cervical spine taken with routine views were reported as negative. Physiotherapy was given without relief. The patient was then admitted for diagnosis and treatment.

Physical examination revealed a well developed, well nourished, 9-year-old white boy whose head was tilted toward the left shoulder and turned toward the right; this position was rigidly maintained and the patient complained of pain with any active or passive motion of the head. There was tenderness on the right side of the neck and just below the occiput. On changing position, such as sitting up from a recumbent position, he protected his head with his hands. The ears, pharynx, mastoids, heart, lungs, and abdomen were negative; there was no lymphadenopathy and the sternocleidomastoid muscles were normal.

Laboratory examinations showed a negative urine examination, Mazzini test, and Mantoux test. The white blood cell count was 9,700 per cubic millimeter. The differential count was normal.

Stereoscopic x-ray views of the cervical spine were taken and reported as negative. However, because the torticollis was so painful, skeletal traction by means of a chin halter with 5 lb. of force was applied with the neck in hyperextension. Meanwhile, review of all roentgenograms showed "definite malalignment and over-riding of the facets on the right side . . . while on the left the usual joint space is visualized." After eighteen days of skeletal traction with the chin halter no improvement was evident, so that patient was taken to the operating room for reduction of the subluxation by manipulation under general anesthesia. Traction was put on the neck, which was then deviated to the side opposite the subluxation (left), the neck and head were then rotated in the direction of the affected side (right). On the third manipulation, a definite "snap" was heard and passive movement was free in all directions. A plaster neck jacket was then applied for a period of ninety-five days, and then removed. The results were excellent, and no further difficulty occurred in a two and one-half year follow-up.

CASE 3.—B. S., a 9½-year-old white girl, was admitted to The New York Hospital in June, 1947, with the complaint of painful torticollis and fever of four days' duration. Her family history was negative. She had had a tonsillectomy at the age of 5½ years. That night she developed a wry neck and was placed in a plaster cast for a two-week period with a good therapeutic result.

Ten days before admission, the patient developed an upper respiratory infection. Four days before admission she had muscular aches, chills, and fever of 105° F. and developed a painful torticollis. She was treated for two days with sulfadiazine without response.

Examination revealed an acutely ill, well-developed and well-nourished girl complaining of pain in her neck. The neck was rotated to the left and the head flexed forward, depressing the chin; active or passive motion of the neck elicited exquisite pain. The pharynx was red and there was a purulent postnasal discharge. The nasal mucosa were also inflamed. Anterior and posterior cervical lymph nodes were palpable bilaterally. There was pain and tenderness on the right side of the neck and over C₁ and C₂ posteriorly. There was a bulge in the posterior pharyngeal wall. The sternocleidomastoid muscles were unremarkable. The rest of the examination was unremarkable.

A white blood cell count on admission was 21,000 per cubic millimeter with 80 per cent polymorphonuclear leucocytes. Mazzini and Mantoux tests were negative.

There was disagreement among the radiologists who interpreted the x-ray films of the cervical spine taken by routine technique. An orthopedic consultant interpreted these x-rays as showing a unilateral anterior subluxation on the right.

The patient was placed in skeletal traction with Crutchfield tongs imbedded into the skull. Two days later she was found apneic and cyanotic, but responded to stimulants and artificial respiration. She was diplopic and stuporous for several hours afterward. The tongs were reimbedded one inch forward to afford greater extension of the neck and maximum patency of the airway. The respiratory infection was treated with parenteral penicillin. Eight days after admission the upper respiratory infection became worse and was complicated by a left otitis media; the pharyngeal bulge was suspected by a consultant as being a subsiding retropharyngeal abscess. Her course was further complicated by an occipital decubitus ulcer.

After twenty-one days of skeletal traction, the tongs were removed and a plaster neck jacket applied. Roentgenograms of the cervical spine at this time were negative. She was discharged from the hospital to be followed in the clinics; three months later the cast was removed and roentgenograms were again negative. There was a full return of flexion, extension, abduction and rotation to the left, but rotation to the right was limited to 45° and there was still some tenderness over C₁ and C₂ on this side.

CASE 4.—D. M. This 8-year-old white girl was admitted to The New York Hospital in October, 1947, with the complaint of painful torticollis of four months' duration. Her father and a brother had hay fever, and the paternal grandfather and an uncle had diabetes. The patient was also known to suffer from hay fever but otherwise her past history has been unremarkable.

Four and one-half months before admission the patient had a sore throat and fever to 104° F.; she was treated by a private doctor with sulfonamide drug and bed rest for ten days. After the drug was discontinued she developed a hot, tender swelling on the right side of the neck which reached its maximum three weeks later. It was painful and the child was noted to keep her head turned to the left and flexed forward. There was no history of trauma. A private doctor made a diagnosis of "mumps" and disregarded the torticollis.

Three and one-half months before admission she took a trip by train and it was noted that the vibration and jarrings of the ride were extremely painful, so that she protected her head with her hands. She was seen by another private doctor and a pediatric consultant who made a diagnosis of "virus infection." An x-ray examination of the cervical spine at this time was interpreted as negative. Physical therapy was given to the neck daily. The torticollis persisted. She was admitted to this hospital for diagnosis and treatment.

Examination revealed a well-developed, well-nourished girl who complained of pain in the right side of the neck with any motion; the head was rigidly turned to the left and slightly forward, depressing the chin. There was pain on lateral flexion, flexion and extension of the neck, rotation past 45 degrees to the left and past the midline to the right, pressure on top of the head, and raising the head off the neck. There was tenderness over C₁ and C₂ on the right and posteriorly. A bulge was palpable in the posterior pharyngeal wall. The sternocleidomastoid muscles were normal. In changing position, she held her head in her hands to protect against sudden movement in the neck. The remainder of the examination was unremarkable.

Routine x-ray views of the cervical spine including those through the open mouth were reported as negative by the radiologists. However, an orthopedic consultant made the diagnosis of nontraumatic subluxation of the atlantoaxial joint on the right. Skeletal traction by chin halter with the neck in hyperextension was started and continued for seventeen days, when it was discontinued during the day because of marked symptomatic improvement, but within five days pain and torticollis returned and continuous skeletal traction was resumed. Because the chin halter was so uncomfortable, it was decided to use Crutchfield tongs; this was done forty-one days after skeletal traction was started by chin halter, and was continued for thirty days more. A plaster cast was applied to immobilize the neck in hyperextension and the patient was discharged to be followed in the out-patient department. Three months later the cast was removed; there was no discomfort and function was normal except for slight limitation of rotation to the left.

GENERAL CONSIDERATIONS

A. *Synonyms of this condition appearing in the literature.—*

Distensionsluxation (Wittek).³

Drehungsverrenkung (Sudek).⁴

Inflammatory dislocation (Fitzwilliams).⁵

Maladie de Grisel (Desfosses).⁶

Non-traumatic subluxation (Berkheiser and Seidler).²

Spontaneous dislocation (Hess).¹

Spontaneous hyperemie dislocation (Watson-Jones).⁷

Torticollis nasopharyngien (Grisel).⁸

B. *Definitions.—*

Atlas: The first cervical vertebra is a ring of bone with short transverse processes, but no body or spine. The anterior portion of the inner aspect of the ring has a shallow groove which forms a joint with the ventral part of the odontoid process. The anterolateral masses of the ring support the facets of the atlanto-axial joints. The superior facets are oval, concave, and support the occipital condyles. The inferior facets are flat and oval, and slant downward, laterally and slightly forward.^{2, 9}

Axis: The second cervical vertebra has two small transverse processes, a heavy spinous process, and a forward shaft of bone called the odontoid process. The superior facets are flat, oval, and slant downward and laterally.^{2, 9}

Atlanto-axial joint: There are four distinct joints between the first and second vertebrae, two of which are related to the odontoid process: the atlanto-odontoid joint, a rotary diarthrosis between the anterior aspect of the odontoid

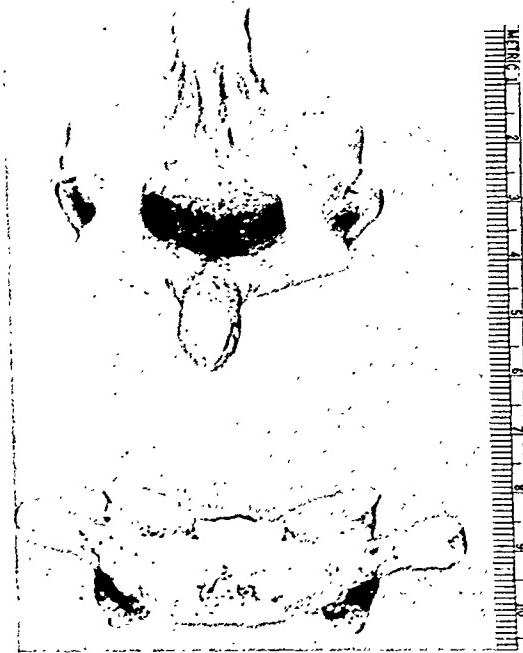


Fig. 1.—Posterior views of the atlas and the axis showing the inclination and flatness of the facets.

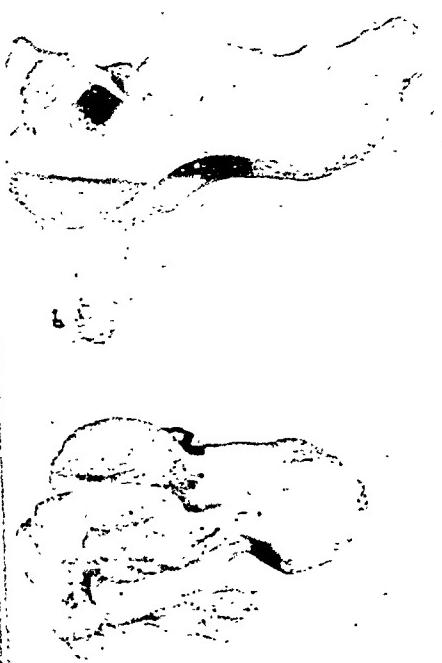


Fig. 2.—Further views of the atlas and the axis showing the nature of their articulating surfaces.

process and the posterior aspect of the anterior arch of the atlas, and the syndesmo-odontoid joint between the posterior aspect of the odontoid process and the transverse ligament. The two lateral arthroidal diarthroses (gliding joints) are the ones with which we are mainly concerned.^{9, 10} They have loose capsules which allow maximum motion,⁹ much of which is rotation (of the neck) but also some lateral movement.¹¹

Dislocation: A disarrangement of the bones entering into the formation of a joint; luxation.¹²

Subluxation: A minor degree of dislocation; an incomplete luxation or dislocation.¹²

Transverse ligament: A heavy ligament attached to the anteriolateral portions of the ring of the atlas and forming the posterior support of the odontoid process.⁹

Details of the anatomy of these two vertebrae are apparent in Figs. 1 and 2. These views clearly demonstrate the flatness and the slanting of the lateral articulations.

REVIEW OF LITERATURE

The earliest case of atlanto-axial subluxation associated with infection of the neck was reported by Bell in 1830.¹³ His patient had a pharyngeal ulcer and died of respiratory failure; post-mortem examination revealed erosion of the transverse ligament and subluxation of the atlas on the axis resulting in pressure on the cord.

In 1903, Böger¹⁴ described a case of unilateral dislocation of the atlanto-axial joint in a 17-year-old boy with acute rheumatic fever. He believed that the articular process had loosened the joint ligaments sufficiently to allow this dislocation.

Wittek,³ in 1908, reported the case of an 11-year-old boy who developed a subluxation of this joint subsequent to periostitis of the jaw. He presumed that the joint ligaments had been stretched, "probably due to a metastatic effusion into the joint between the odontoid and the anterior atlas ring on one side and between the odontoid and the cruciate ligaments on the other side, and also in the inferior articulations between the atlas and the axis."

Jacobs,¹⁵ in 1918, accepted Wittek's theory of "metastatic effusion into the atlanto-axial joint" and compared this type of subluxation with that seen occasionally in cases of typhoid fever complicated with subluxation of the hip. He stressed the threat of cord injury in dislocation of the atlas, especially when it was associated with a fracture of either of the first two cervical vertebrae.

Swanberg,¹⁶ in 1919, reported the case of a 22-year-old soldier who developed painful torticollis following a tonsillectomy. He thought that the transverse ligament of the axis had ruptured, releasing the posterior odontoid support thereby predisposing the joint to subluxation.

Sudek,⁴ in 1923, thought the etiology in one of his cases to be excessive passive rotation of the neck while under deep anesthesia for an operation on the neck.

Greig,¹⁷ in 1931, suggested that hyperemia due to the adjacent inflammatory process caused decalcification of the vertebrae, especially about the ligamentous attachments, thereby relaxing the ligaments of the joint. Leriche and Pollicard¹⁸ demonstrated this principle experimentally, showing the decalcification of bone with increased blood supply, and its sclerosis with ischemia.

Watson-Jones⁷ presented roentgenographic evidence of this mechanism in 1931. His patient was a 9-year-old boy who developed torticollis as a complication of acute mastoiditis; the lateral view of a roentgenogram of the cervical spine failed to reveal the anterior arch of the atlas but showed subluxation of this joint. Three months later, when the infection had subsided, the anterior arch was again calcified. Watson-Jones postulated that the decalcification had loosened the ligamentous attachments of the joint, facilitating avulsion of the transverse ligament without fragmentation of the atlas.

Grisel,⁸ in 1930, proposed the theory that irritative contracture of the suboccipital and paravertebral muscles following cervical lymphadenitis due to a nasopharyngeal infection caused the subluxation. Tedesco, Grisel, Desfosses, and Tassin¹⁹ published the first report on the subject in a pediatric journal in 1930.

Berkheiser and Seidler² in 1931 favored Wittek's theory of metastatic effusion into the joints and added that the anterior and posterior bursae were involved in and contributed to the predisposition to subluxation. They pointed out that the forward position of the center of gravity of the head and the forward slanting of the facets predisposed this joint to forward subluxation.

Hess and associates¹ in 1935 concluded that the "production of the atlanto-axial dislocation involves a combination of factors, the *sine qua non* being weakening of the lateral ligaments. Spasm of the cervical muscles in association with loose ligaments is a feasible mechanism. Nevertheless, it appears more likely that the dominant role played by the spasm is the prevention of spontaneous and easy reposition, with resulting locking of the overlapping edges."

Brav²⁰ in 1936 reported an interesting case of voluntary subluxation of this joint by a 29-year-old man who used this peculiar ability for illegal gain.

SYMPTOMS AND FINDINGS

Typically with this condition there will have been an inflammatory process in or about the neck, most frequently in the nasopharynx, from one day to several weeks before the onset of the torticollis.^{1, 2} When the torticollis starts during the acute phase of a severe cervical infection, it is frequently presumed to be due to protective spasm until this symptom persists after the acute process recedes. The subluxation may have been precipitated during sleep,²¹ following a sharp jar as a slap on the back²² or throwing a baseball,²³ or during passive motion of the neck under anesthesia.²⁴ This type of subluxation is very painful and is aggravated by jarring or sudden movement of the head so that the patient limits his activity and protects his head with his hands when changing position.^{1, 2}

The symptoms depend upon the type of subluxation present, three types of which are possible: anterior unilateral, anterior bilateral, and posterior unilateral. Posterior bilateral subluxation of the atlas on the axis is theoretically impossible in the presence of an intact odontoid process and transverse ligament.²

Patients with anterior unilateral subluxation present the following picture: the neck is rotated away from the subluxated side; the head is tilted toward the affected side and flexed anteriorly so that occasionally the mouth cannot be opened sufficiently to allow palpation of the nasopharynx; this position is rigidly maintained. In some instances the shoulder on the affected side may be elevated. A nasal quality of the voice has been described with this condition and is thought to be related to the partial obliteration of the nasopharynx by the anterior arch of the atlas, which is displaced forward and can be palpated as a bulge in the posterior pharyngeal wall.¹ Tenderness is palpable over the subluxated joint laterally and posteriorly over C₁ and C₂.²⁵ The spinous process of the axis is frequently palpable away from the midline toward the affected side (Sudek's sign)⁴ due to the counter-rotation of this vertebra. The rotation of the atlas and axis in opposite directions results in detectable cervical scoliosis.^{1, 2} Root and cord signs have been infrequently reported with this syndrome. However, Wilson²⁶ reported a case of a 62-year-old woman with unilateral atlanto-axial subluxation following an upper respiratory infection who developed quadriplegia and other neurological symptoms which were completely relieved by skeletal traction. Woltman²⁷ described the case of a 14-year-old boy who developed an anterior unilateral subluxation as a sequel to pharyngitis and six months later sustained a bilateral anterior subluxation complicated by numbness and weakness of the extremities following a fall. Immobilization by cast relieved the symptoms.

In patients with a posterior unilateral subluxation, the neck is rotated toward the affected side, Sudek's sign is positive on this side, and there is no pharyngeal bulge.^{1, 2}

If anterior bilateral subluxation is present, there is little or no rotation of the neck, the head is tilted forward, motion is markedly limited in all directions, and the pharyngeal bulge is most prominent.²

Patients with this syndrome have been reported from 2 to 62 years of age. Wilson²⁶ reviewed twenty-eight acceptable cases and found that 85.6 per cent of patients were under 13 years of age. An analysis of fifty-six cases including those reviewed and those reported here, shows that 76.8 per cent of patients were under 13 years of age; the average age was 12.2 years.

Of fifty-two acceptable cases of nontraumatic subluxation of the atlanto-axial joint, including those reviewed and those reported here, 46 per cent occurred in male and 54 per cent in female patients. The average age was 13.0 years for male and 11.6 years for female patients.

X-RAY DIAGNOSIS

A consideration of the use of x-ray in this condition is most important since so frequently the routine x-ray film is reported as negative when indeed

a subluxation exists as judged by symptoms and examination and is demonstrable by special x-ray techniques. Swanberg¹⁶ reported the case of a 22-year-old soldier who had had six roentgenograms of the neck for persistent torticollis, all of which were reported negative; the condition remained undiagnosed for six months. Swanberg (1919) stated, "this is the second case of anterior dislocation of the atlas I have observed that has not been recognized by the roentgenogram." Since this complaint in 1919 the same thought has been repeatedly reiterated in the literature on this subject. At The New York Hospital at least two cases of subluxation of this joint, undiagnosed for more than one year, have been seen, in which several x-rays were reported as negative.



Fig 3.—A reproduction of an x-ray view in the anteroposterior position through the opened mouth showing unilateral subluxation on the right. Note the shortening of the facets on the affected side with displacement of the odontoid process to the opposite side.

Technically, this joint is difficult to study roentgenographically.^{2, 28} The routine examination includes the anteroposterior view through the open mouth and lateral views. The former is more important in mild subluxations, but when the chin is depressed forward sufficiently to interfere with opening of the mouth, it is difficult to obtain. Lateral views frequently show no abnormality since displacement of the atlas is minimal in this type of subluxation.²⁹

Stereoscopic views are preferred, especially in children whose immature bony structures may have appearances which mimic fractures due to the numerous ossification centers and areas of incomplete fusion.²⁸

The Morgan Meter³⁰ is occasionally useful. It utilizes the formula: Intensity \times Exposure Time = Constant. It is also useful for x-ray views through plaster casts as well as for deep structures.

Jostes³¹ (1942), reporting results with the laminograph described by Dr. Sherwood Moore³² and Mr. Keifler of Connecticut, stated that "the cervical vertebrae can be studied and understood roentgenographically only by means of this body section method." He states further that this usually discloses dislocations of the occipito-atlas and atlanto-axial joints missed by other techniques. He presents photographic evidence to substantiate his contention. His interest in the use of the laminograph started after he saw several patients with persistent neck pain with negative routine cervical roentgenograms who responded therapeutically to skeletal traction and who showed minor changes by the laminograph. Dr. Moore had previously stated that "upper cervical traumas and anomalies are a bane of the radiologist when he is limited to conventional methods or stereoscopic films from different angles; there is a need for something additional. This is fulfilled by the laminograph."

In the positive roentgenogram in the anteroposterior view through the open mouth, there is reduction or disappearance of the joint space on the affected side, often with overlapping of the facets. There may be some lateral displacement of the odontoid process. In the lateral view there may or may not be detectable anterior displacement of the body of the atlas.^{1, 20}

TREATMENT

Subluxation of the atlanto-axial joint is sometimes susceptible to treatment by manipulation under anesthesia by the method of Walton,³³ in which the neck is hyperextended, its tilt and rotation exaggerated, and as traction is applied to the head with countertraction to the shoulders, the head is slowly rotated toward the midline. This method does not always reduce the subluxation and may be dangerous in inexperienced hands or in the presence of a fracture or avulsion of the transverse ligament. Reduction by manipulation should be followed by immobilization in a leather collar or plaster neck jacket.

In most cases, however, permanent results will require a skeletal traction in hyperextension by means of a chin halter or Crutchfield tongs imbedded in the skull. Elevation of the head of the bed by shock blocks makes use of gravity for countertraction. Hyperextension of the neck may be effected by use of a second mattress atop the first so placed that the head falls over one end of the upper one as the patient lies supine. Skeletal traction is continued until clinical and x-ray evidence of subluxation disappear; this varies from two to four weeks. Following reduction by manipulation or traction, immobilization in the reduced position is secured by a plaster cast, Thomas collar, or similar device.^{1, 2, 20} Bisgard³⁴ (1932) described a device for the simultaneous traction and complete immobilization of the cervical spine.

Some authors report spontaneous subluxation followed by spontaneous reduction. Swanberg's case was suspended by the head, using the body's

weight for the traction force after manipulation under general anesthesia had failed; this attempt also failed and continuous skeletal traction had to be employed.

In cases with neurologic symptoms, skeletal traction alone is usually adequate treatment, though cord decompression may be necessary.^{35, 36}

Gillette³⁷ reported cases of nontraumatic torticollis improved by tonsillectomy.

SUMMARY OF REPORTED CASES OF NONTRAUMATIC SUBLUXATION OF THE ATLANTO-AXIAL JOINT CONSIDERING AGE, SEX, AND ASSOCIATED INFLAMMATORY PROCESS

AUTHOR	YEAR	AGE (YR.)	SEX	INFLAMMATORY PROCESS
Berkheiser and Seidler ²	1931	9	F	Influenza
Blunch ³⁹	1935	10	M	Fever
Brookes and Ewerhardt ⁴¹	1932	19	F	Tonsillar abscess
Chesterman ⁴²	1936	10	F	Tonsillitis
Desfosses ⁶	1930	7	F	Nasopharyngitis
Englander ⁴³	1942	7	F	Tonsillitis and adenitis
Enrique Rivarola ⁴⁴	1938	8	M	Cervical abscess
		15	?	Otitis media
Frank ⁴⁵	1931	9	M	Retropharyngeal abscess
Fitzsimmons ⁴⁶	1915	8	F	Pharyngitis and adenitis
Fitzwilliams ⁵	1934	10	M	Coryza and adenitis
Garcia-Diaz ⁴⁷	1940	9	F	Cervical abscess
Gillette ³⁷	1896	3	?	Cold
Grisel ⁸	1930	8	F	Tonsillitis
		9	F	Nasopharyngitis
Hauflig and Schlosberg ¹⁸	1940	7	M	Nasopharyngitis and adenitis
Hess and associates ¹	1935	6	M	Scarlet fever and adenitis
		11	F	Coryza
Iloikkila ⁴⁹	1937	17	M	Parotitis
Jacob ⁹	1918	5	M	Fever
Llambria ⁵⁰	1940	10	F	Nasopharyngitis
Martin ⁵¹	1942	6	M	Mastoiditis and adenitis
Maxwell ⁵²	1947	10	F	Pharyngitis and cervical adenitis
Piotet ⁵³	1934	8	F	Retropharyngeal abscess
Sudek ⁴	1923	8	F	Pharyngitis and adenitis
Swyngedauw, Bonte and Laine ⁵⁴	1942	10 $\frac{1}{2}$	F	Otitis media
		8	F	Cervical adenitis and fistula
Watson-Jones ⁷	1931	16	F	Tuberculous adenitis
		2	?	Pharyngitis
		9	M	Mastoiditis
Wilson and associates ²⁶	1940	62	F	Upper respiratory disease
Weissberg and Reinstein ⁵⁵	1940	52	M	Coryza
Wittke ³	1908	11	F	Alveolar abscess
Woltman and Meyerding ²⁷	1934	14	M	Tonsillar abscess
Zeilter and Odessky ⁵⁶	1934	12	F	Parotitis and influenza
Dennison ⁵⁷	1939	5 $\frac{1}{2}$	M	Following mastoidectomy
Fitzsimmons ⁴⁶	1915	11	F	Following mastoidectomy
Jones ⁸	1931	10	M	Following tonsillectomy
Martin ⁵¹	1942	6	M	Following mastoidectomy
Maxwell ⁵²	1947	14	M	Following mastoidectomy
		6	F	Following mastoidectomy
Odellberg Johnson ⁵⁸	1932	16	F	Following tonsillectomy
Steel ⁵⁹	1937	7	M	Following adenoidectomy
Swanberg ¹⁶	1919	22	M	Following tonsillectomy
Tedesco and associates ¹⁹	1930	11	F	Following mastoidectomy
		12	F	Following mastoidectomy
Berkheiser and Seidler ²	1931	8	F	Acute rheumatic fever
Bioger ¹⁴	1903	17	M	Acute rheumatic fever
Ely ¹	1911	13	M	Acute rheumatic fever
Evans ²	1911	9	M	Acute rheumatic fever
Fitzwilliams ⁵	1934	15	M	Acute rheumatic fever
Foxe and Friedman ⁶⁰	1930	35	M	Chronic rheumatoid arthritis

PROGNOSIS

In unilateral subluxation, the prognosis is good with adequate treatment. Without treatment, the patient's appearance may be markedly affected. Hess and associates,³⁵ in a five-year follow-up of one of their original cases in which treatment had been refused, found moderate asymmetry of the face, rotation of the head, prominence of the infraspinous muscles, limitation of motion of the neck, and a positive Sudek's sign. The mouth, which had previously been impossible to open, could now be opened fully. Incidentally, this patient had been seen by several physicians and a chiropractor who doubted the diagnosis because of a negative history of trauma.

There are two reports in the literature of anterior unilateral subluxation being converted into anterior bilateral subluxation following moderate trauma; both of these patients developed symptoms of cord compression which, though not fatal, were incapacitating.^{23, 27} However, the proximity of this joint to the respiratory center of the medulla increases the hazard of this syndrome. Though the episode of apnea, cyanosis, and later diplopia in Case 3 remains unexplained, one wonders if it was not due to compression of the medulla.

SUMMARY AND CONCLUSIONS

1. Nontraumatic subluxation of the atlanto-axial joint is not a frequent occurrence, but is an important cause of persistent torticollis in the pediatric age group.
2. It is usually preceded by an infection in the tissues of the neck, including coryza, pharyngitis, pharyngeal abscess, cervical adenitis and abscess, otitis media, mastoiditis, parotitis, etc.
3. The mechanism of subluxation appears to be related to metastatic effusion into the joint causing distention and relaxation of the capsule and joint ligaments; subluxation is precipitated by spasm of the paravertebral muscles, minor trauma, or passive manipulation as in anesthesia or sleep.
4. Three types of subluxation occur: (a) anterior unilateral, (b) posterior unilateral, and (c) anterior bilateral.
5. Common symptoms are: pain and tenderness over the subluxated joint, worse with jarring and rigidity of the neck. In the anterior unilateral type, the chin is depressed and the neck is rotated away from the subluxated side. There is a pharyngeal bulge and Sudek's sign is present on the opposite side. In posterior unilateral subluxation, the head is tilted toward the subluxated side, there is no pharyngeal bulge, and Sudek's sign is present on this side. In the anterior bilateral type, the head is held more or less rigidly close to the midline, the chin is depressed, Sudek's sign is negative, and there is a marked pharyngeal bulge.
6. Neurologic symptoms are unusual, and when present, bilateral subluxation or fracture of the odontoid process must be considered.
7. X-ray visualization of this region is not dependable by routine methods. A negative report does not preclude the absence of a subluxation.

8. Prognosis for recovery is good for function and facial symmetry if treated early and adequately.

9. Treatment consists of manipulation under general anesthesia or skeletal traction with the neck in hyperextension followed by immobilization with a plaster cast or leather collar.

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REFERENCES

1. Hess, J. H., Abelson, S. M., and Bronstein, I. P.: Atlanto-Axial Dislocation Unassociated With Trauma and Secondary to Inflammatory Foci of the Neck, *Am. J. Dis. Child.* 49: 1137, 1935.
2. Berkheiser, E. J., and Seidler, F.: Non-Traumatic Dislocations of the Atlanto-Axial Joint, *J. A. M. A.* 96: 517, 1931.
3. Wittek, A.: Ein Fall von Distensionsluxation im atlanto-epistropheal Gelenke, *Munchen. med. Wchnschr.* 55: 1836, 1908.
4. Sudek, P.: Ueber Drehungsverrenkung des Atlas, *Deutsche Ztschr. f. Chir.* 183: 289, 1923.
5. Fitzwilliams, D. C. L.: Inflammatory Dislocation of the Atlas, *Brit. M. J.* 2: 107, 1934.
6. Desfosses, R.: Un Cas de Maladie de Grisel: Torticollis Nasopharyngien par Subluxation de l'Atlas, *Presse Méd.* 38: 1179, 1930.
7. Watson-Jones, R.: Spontaneous Hyperemic Dislocation of the Atlas, *Proc. Roy. Soc. Med.* 25: 586, 1932.
8. Grisel, P.: Enucleation de l'atlas et torticollis nasopharyngien, *Presse Méd.* 38: 50, 1930.
9. Gray, Henry: Anatomy of the Human Body, ed. 25, edited by Charles Mayo Gross, 1948.
10. Corner, E. M.: Rotatory Dislocation of the Atlas, *Ann. Surg.* 45: 9, 1907.
11. Dankmeijer, J., and Dethmeijer, B. J.: The Lateral Movement in the Atlanto-Axial Joints and Its Clinical Significance, *Acta Radiol.* 24: 55, 1943.
12. Stedman's Medical Dictionary, 14th Revised Edition, Baltimore, 1939, Williams & Wilkins Company.
13. Bell, Sir Charles: The Nervous System of the Human Body, Embracing the Papers Delivered to the Royal Society on the Subject of the Nerves. No. 118, page 403, 1830.
14. Böger: Ein Fall von malum suboccipitale Rheumaticum, *Arch. f. Orthop. Mechanotherap. u. Unfall-Chir.* 3: 97, 1903.
15. Jacobs, Charles: Atlas and Axis Subluxation, *Am. J. Ortho. Surg.* 16: 357, 1918.
16. Swanberg, H.: Anterior Dislocation of the Atlas Following Tonsillectomy, *J. A. M. A.* 72: 107, 1919.
17. Greig, D. M.: Clinical Observations on the Surgical Pathology of Bone, Edinburgh, 1931, Oliver and Boyd.
18. Leriche, R., and Policard, A.: Les problèmes de la physiologie normale et pathologique de l'os, Paris, 1926, Masson et Cie.
19. Tedesco, P., Grisel, P., Desfosses, P., and Tassin, M.: Deux nouveau cas d'enucleation de l'atlas par torticollis nasopharyngien, *Bull. Soc. pediat. de Paris* 28: 252, 1930.
20. Bray, E. A.: Voluntary Dislocation of the Neck: Unilateral Rotatory Subluxation of the Atlas, *Am. J. Surg.* 32: 144, 1936.
21. Brookes, T. P.: Dislocation of the Cervical Spine—Some Predisposing Factors, *J. A. M. A.* 104: 902, 1935.
22. Mixter, S. J., and Osgood, R. B.: Traumatic Lesions of the Atlas and Axis, *Ann. Surg.* 51: 193, 1910.
23. Ogilvy, Charles: Subluxation of the Atlas Upon the Axis, *Am. J. Orth. Surg.* 12: 314, 1914-1915.
24. Barnett, J. B.: Cervical Subluxation Following Anesthesia, *Brit. Med. J.* 1: 1077, 1929.
25. Martin, R. C.: Dislocation Following Cervical Infection, *Pacific Coast Oto-Ophth. Soc.* 25: 217, 1940.
26. Wilson, M. J., Michele, A., and Jacobson, E.: Spontaneous Dislocation of the Atlanto-Axial Articulation Including a Report of a Case With Quadriplegia, *J. Bone & Joint Dis.* 22: 698, 1940.
27. Wolman, H. W., and Meyerding, H. W.: Spontaneous Hyperemic Dislocation of the Atlanto-Axial Joint, *Surg. Clin. North America* 14: 581, 1934.

28. Hickey, P. M.: Lateral Roentgenography of the Spine, Am. J. Roentgenol. 4: 101, 1917.
29. Leibolt, Frederick, M.D.: Personal communication.
30. Morgan, R. H.: A Photoelectric Timing Mechanism for the Automatic Control of Roentgenographic Exposure, Am. J. Roentgenol. 48: 220, 1942.
31. Jostes, F. A.: Neck Pain: The Laminograph as an Aid to the Diagnosis of Atlanto-Axial Lesions, J. A. M. A. 118: 353, 1942.
32. Moore, Sherwood: Body Section Radiography, Radiol. 33: 605, 1939.
33. Walton, G. L.: A New Method of Reducing Dislocation of the Cervical Vertebrae, J. Nerv. & Ment. Dis. 20: 609, 1893.
34. Bisgard, J. D.: A Device for the Simultaneous Traction and Complete Immobilization of the Cervical Spine, J. Bone & Joint Surg. 14: 180, 1932.
35. Kahn, E. A., and Iglesias, L.: Progressive Atlanto-Axial Dislocation, J. A. M. A. 105: 348, 1935.
36. Schwartz, G. A., and Wigton, R. S.: Fracture Dislocations in the Region of the Atlas and Axis With Consideration of Delayed Neurological Manifestations and Some Roentgenographic Features, Radiol. 28: 601, 1937.
37. Gillette, W. J.: Torticollis Due to Adenoid Vegetation and Chronic Hypertrophy of the Tonsils, New York Med. J. 64: 155, 1896.
38. Hess, J. H., Abelson, S. M., and Bronstein, I. P.: Spontaneous Atlanto-Axial Dislocation: Possible Relation to Deformity of the Spine, Am. J. Dis. Child. 64: 51, 1942.
39. Blunck, C.: Ueber die Atlasluxation, Beitr. z. klin. Chir. 162: 285, 1935.
40. Brinckman, Erich: Die Drehungsverrenkung des Atlas, Klin. Wehnschr. 7: 649, 1928.
41. Brookes, T. P., and Ewerhardt, F. H.: Reducing and Treating Cervical Dislocations, Arch. Phys. Therapy 13: 463, 1932.
42. Chesterman, J. T.: Spontaneous Subluxation of the Atlanto-Axial Joint, Lancet, 1: 539, 1936.
43. Englander, O.: Non-Traumatic Occipito-Atlanto-Axial Dislocation, Brit. J. Radiol. 15: 341, 1942.
44. Enrique Rivarola, Jose: Sabre un caso de enfermedad de grisel, Prensa Médica Argentina, 25: 138, 1938.
45. Frank, Ira: Spontaneous Non-Traumatic Atlanto-Axial Subluxation, Ann. Otol. Rhin. and Laryng. 45: 405, 1936.
46. Fitzsimmons, H. J.: Four Cases of Unilateral Rotatory Displacement of the Cervical Spine, Interstate Med. J. 22: 953, 1915.
47. Garcia-Diaz, C. J.: Torticollis por Subluxation Atloaxoiden Grisel's Disease, La Semana Medicina 2: 1289, 1940.
48. Haufnig, S. S., and Schlosberg, C.: Non-Traumatic Dislocation of the Atlanto-Axial Joint, New England Med. J. 223: 713, 1940.
49. Heikkila, V.: Inflammation of the Atlanto-Axial Joint: A Sequel of Epidemic Parotitis, Duodecim 53: 475, 1937.
50. Llambia, Alfredo: Consideraciones Acerca del Torticollis Nasofaringeo, Revista de la Asociacion (de Medicina Argentin) 34: 473, 1940.
51. Martin, R. C.: Atlanto-Axis Dislocation Following Cervical Infection, J. A. M. A. 118: 874, 1942.
52. Maxwell, J. H.: Otolaryngological Aspects of Wry Neck, Translations, Am. Acad. Ophth. and Otolaryg., p. 51, 1947.
53. Piotet: A Rare Complication in the Removal of the Adenoids: A Case of Nasopharyngeal Torticollis, Achweiz. med. Wehnsehr. 64: 355, 1934 (Abstracted in J. A. M. A. 102: 2070, 1934).
54. Swynghedauw, P., Bonte, G., and Laine, E.: Presentation de planigraphies dans 4 cas d'osteo-arthrite des premières vertèbres cervicales, secondaire à une suppuration latérocervicales, J. de Radiol. et d'Electrol. 25: 206, 1942-1943.
55. Weissberg, J., and Reinstein, H.: Spontaneous Dislocation of the Atlanto-Axial Articulation, The New York M. Coll. and Flower Hosp. Bull. 3: 306, 1940.
56. Zeitzer, A., and Odessky, J.: La Subluxation Atlanto-Axoidienne d'Origine Nasopharyngienne, Arch. de med. d'enf. 37: 471, 1934.
57. Dennison, W.: Spontaneous Dislocation (Hyperemic) of the Atlas, Glasgow Med. J. 132: 191, 1939.
58. Jones, A. R.: Dislocation of the Neck at the Atlanto-Axial Joint, Proc. Roy. Soc. Med. 26: 136, 1932.
59. Odelberg-Johnson, G.: A Case of Cervical Spondylarthritis After Tonsillectomy, Acta Orthop. Scandinav. 2: 302, 1932.
60. Steele, G. H.: Spontaneous Dislocation of the Atlas, Lancet 1: 441, 1937.
61. Ely, L. W.: Subluxation of the Atlas, Ann. Surg. 54: 20, 1911.
62. Evans, W.: Pathologic Dislocations of the Atlanto-Axial Joint: An Unusual Complication of Rheumatic Fever, Radiol. 37: 347, 1941.
63. Foxe, A. N., and Friedman, L. J.: Simple Lateral Luxation of the Atlas, Am. J. Surg. 8: 831, 1930.

LIPOID NEPHROSIS COMPLICATED BY HOMOLOGOUS SERUM JAUNDICE

ARTHUR H. ROSENBLUM, M.D., HERMAN LANDER, M.D., AND
HANS POPPER, M.D., PH.D.
CHICAGO, ILL.

THIS report deals with a case of a child with clinically pure lipoid nephrosis who died from homologous serum jaundice during a period of remission. Since plasma has been used extensively in the treatment of the nephrotic syndrome, this combination may become increasingly frequent.

A. B., a 3-year-old white female child, entered the Children's Division of the Cook County Hospital on Nov. 12, 1946, with a history of insidious onset of edema and ascites approximately one month in duration. She had been perfectly well except for measles and chicken pox during the first year of life and pertussis during the second year. There was no history of an antecedent illness, either of a chronic or acute nature, which may have precipitated the disease.

On physical examination the child showed the characteristic appearance of a nephrotic with a moderate amount of generalized pitting edema, ascites, and pallor. There were no other significant physical findings except for a palpable, nontender liver. The urine showed 4 plus albumin, specific gravity 1.034, acid reaction, no sugar or acetone, no blood to chemical or microscopic test, and a few pus cells in the centrifuged sediment. The complete blood count was within normal limits, with a hemoglobin concentration of 13.5 Gm. (Sahli), and a red count of 4.41 millions. The total serum protein concentration was reduced to 4 Gm. per 100 c.c. with reversal of albumin-globulin ratio; the nonprotein nitrogen was 37 mg. per 100 c.c. The sedimentation rate was 30 mm. per hour (Wintrobe). The Kahn test was negative.

The clinical course (Fig. 1) showed a progressive increase in edema and ascites until the seventy-third hospital day, when weight loss began. At various times during the first half of her hospital stay (from the tenth to the fifty-third day), the child received infusions of concentrated pooled human plasma with no appreciable change in her edema. She was given one-half of a Mercupurin suppository on the thirty-first, thirty-seventh, and fiftieth hospital days with little effect. On the fifty-third hospital day, one-half cubic centimeter Mercupurin injected intravenously caused a transient weight loss of 1.5 pounds. From the seventy-eighth to the eighty-fourth hospital day, salt-poor human albumin was injected daily in amounts of 25 to 35 c.c. The subsequent weight loss was rapid and pronounced. However, there was a mild diuresis prior to the institution of this therapy, and it cannot be stated with certainty that the response was produced by the therapy. On the eighty-fifth day, at which time the child appeared edema-free, the total proteins had risen to 5.1 Gm. per 100 c.c.

The liver remained enlarged during the entire hospital stay, but not tender. Just prior to her hospital discharge, the cephalin flocculation was 0

From the Nephritic Service of Children's Division, Department of Pathology, and The Hektoen Institute for Medical Research of Cook County Hospital and Department of Pediatrics and Pathology, Northwestern University Medical School.

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and the thymol turbidity 5.3. The blood pressure was occasionally moderately elevated, 130/85 on the sixty-eighth hospital day, and 112/78 on the eighty-fourth hospital day. However, the significance of such occasional deviations from the normal is questionable, particularly as the child was fearful of blood pressure determinations. Urea clearance tests showed 95 per cent of normal on the twenty-ninth hospital day, and 100 per cent on the thirty-third hospital day.

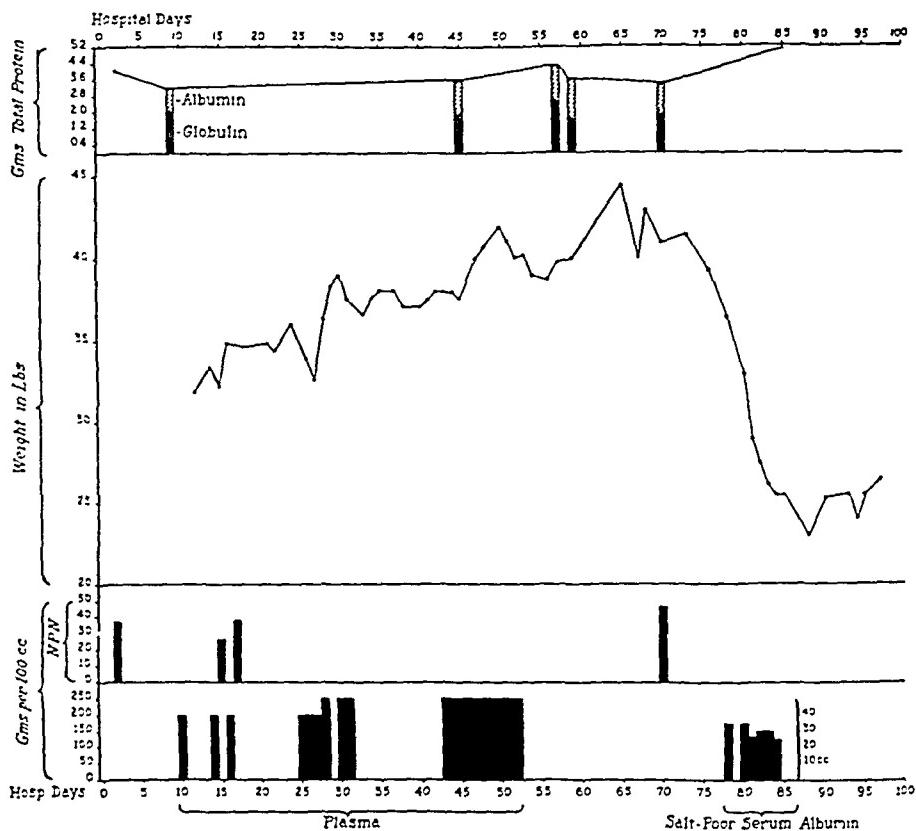


Fig. 1.—Chart indicating the clinical course of the child during first hospital stay.

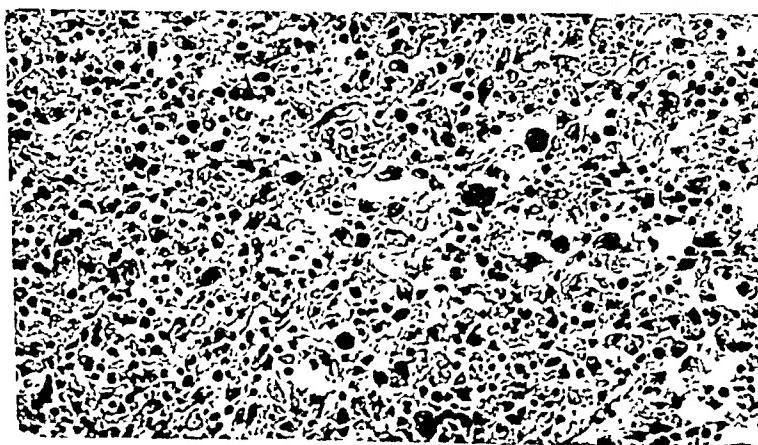
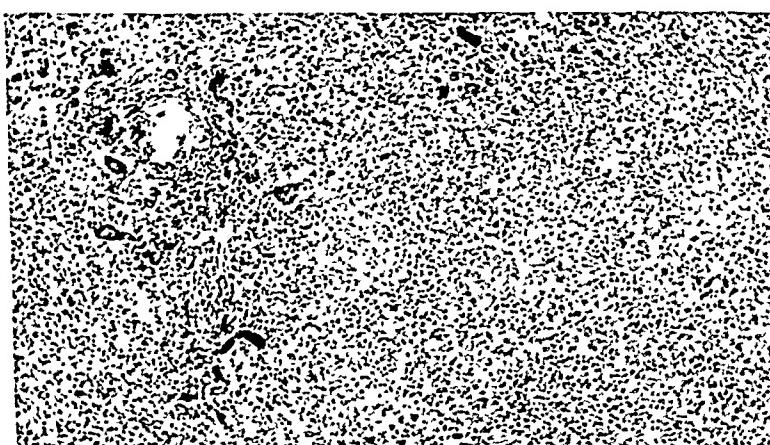
On the ninety-seventh hospital day, the twenty-four-hour urine specimen showed only 270 mg. albumin. At no time during her hospital stay or in subsequent clinic visits did her urine show blood, using the benzidine and orthotolidine tests. On one specimen, an occasional red cell was noted in the centrifuged urine. The nonprotein nitrogen remained consistently within normal limits except for a finding of 46 mg. per 100 c.c. on the seventieth hospital day, at which time the anasarca was close to its maximum.

Subsequent to release from the hospital on the ninety-eighth day after admission, this child was seen in the Clinic on Feb. 28, 1947, and March 28, 1947, in excellent condition. Her weight remained stationary, slightly above that on discharge from the hospital. It was felt that the slight increase could be ascribed to improved nutrition. Her blood pressure was 110/60 on February 28, and 105/60 on March 28. Urine showed one plus albumin and occasional white but no red cells.

On April 6, 146 days after her first admission, the child was again brought to the hospital. This time she was comatose, and markedly jaundiced, but showed no edema. She vomited considerably. She had been febrile for one week, and had been taking a sulfa medication for five days. Four days prior to admission her urine became brown and her skin yellow. A few hours after admission to the hospital the patient died.

Autopsy.—The peritoneal cavity contained approximately 50 c.c. of a sanguineous, yellow fluid. The lungs were dark purple-red, congested, and edematous. The pleura revealed multiple ecchymoses. Trachea and bronchi contained some sanguineous, mucopurulent material. The heart was of normal size, the myocardium pale, the mitral valve edematous. The purple-blue spleen weighed 75 grams and was of reduced consistency. The architecture on the cut surface was somewhat obscured.

A.



B.

Fig. 2.—Photomicrograph of liver revealing fulminant infectious hepatitis.

A, Low-power view. The central veins are closer to the portal triads than normal. The liver cells are missing, except for cords mostly near the portal triads which resemble proliferative bile ducts. The lobular framework is crowded by histiocytic elements. There is dense cellular infiltration of the portal triads.

B, High-power view. In the lobular framework, no liver cells are seen but many mononuclear cells, the larger of which contain bile pigments and phagocytosed material.

Histologically, the large follicles had small germinative centers; the pulp revealed marked reticulum and endothelial cell hyperplasia. The pale pink liver weighed 550 grams. Its inferior edge was sharp. The consistency was unusually low and the organ flattened out if placed on a table. The architecture was mostly obscured; only in circumscribed areas was it well preserved or even exaggerated due to a distinct red color of the lobular centers. The histologic structure of the liver cell cords was entirely missing. However, the arrangement of the central and peripheral fields was well preserved although the fields were closer to each other than usual (Fig. 2, A). The liver cells within the lobules were almost entirely missing. Only toward the periphery were a few isolated polygonal liver cells seen, which revealed diffuse coagulation necrosis of the cytoplasm and occasionally small fat droplets. On the lobular periphery

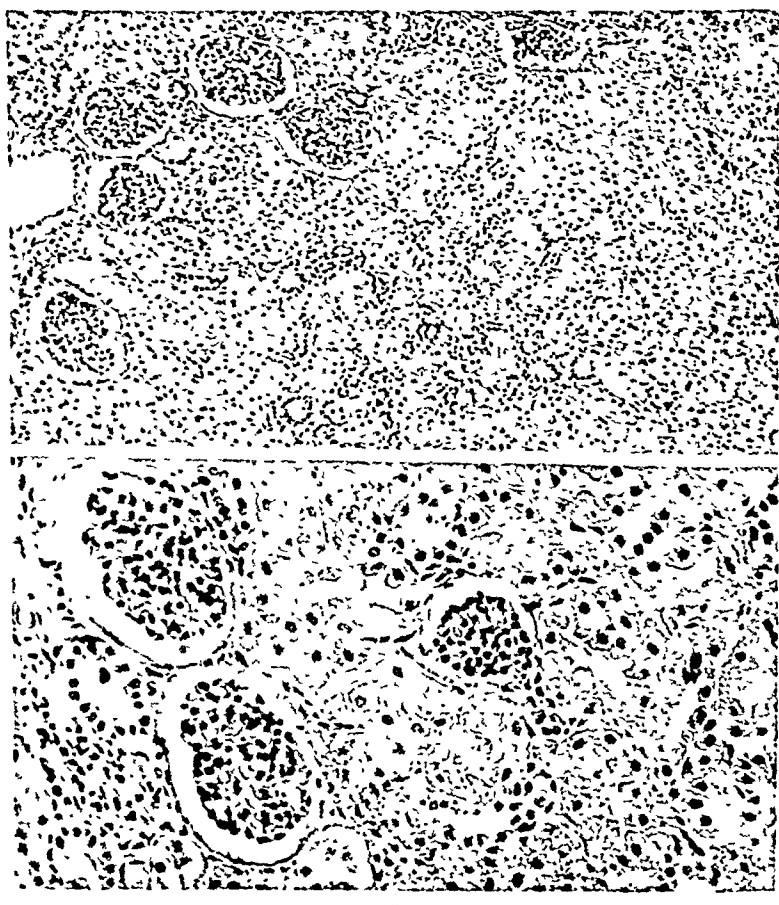


Fig. 3.—Photomicrograph of kidney of child dying about two months after remission of clinically established pure lipid nephrosis.

A. Low-power view. The architecture is intact. The cell content of the glomeruli appears normal. Some albuminoid granules are found in the lumen of the tubules.

B. High-power view. There are some focal adhesions of glomerular loops with proliferation of the peritubular fine vacuoles (after fat extraction) are noted on the base of the epithelial cells of the proximal convoluted tubules.

liver cells were arranged in irregular cords which often revealed a wide bile capillary in their center. These cords simulated proliferated bile ducts. The meshes of the intralobular connective tissue framework were crowded with mesenchymal cells, the larger of which revealed a superficial similarity to liver cells. They contained granular bile pigment and phagocytosed cell fragments. In addition, smaller mononuclear cells were seen, such as lymphocytes and histiocytes. The segmented leucocytes were mostly eosinophilic (Fig. 2, B). In the portal triads and to a lesser degree around the central vein, there was a dense infiltration of similar, round, cellular elements, many of them pigment carrying. The slightly dilated sinusoids contained a moderate number of red cells. A few were also seen in the tissue spaces. The reticular fiber framework was intact; in a few places it was collapsed but nowhere scarred. The widened gall bladder bed was edematous. The portal lymph nodes were markedly enlarged and revealed extensive reactive hyperplasia. Pancreas and lipoid-rich adrenals revealed no abnormalities. The pale pink-gray kidneys were large, weighing together 150 grams. Their surface was smooth. On the cut surface the markings were well recognized. Histologically the architecture was intact (Fig. 3, A). The glomeruli revealed, in general, normal cell content. Only occasionally some glomerular loops appeared matted together and were surrounded by a continuous layer of small cells with dark nuclei in palisade arrangement (Fig. 3, B). The pericytes appeared in places proliferated; nowhere however, did the endothelial cells show proliferation. The basement membrane was mostly normal although in some loops it appeared thickened and the hematoxylin-eosin sections appeared diffusely red. In MacGregory or glycoprotein stains, such loops revealed a double contour of the basement membrane. The tubular epithelium was normal except for regularly arranged, fine vacuoles (apparently after dissolution of fat) on the base of the epithelium of the proximal convoluted tubules (Fig. 3, B). There was no albuminous material in Bowman's space but some in the tubular lumen in form of densely staining granules. Vessels and interstitial tissues were normal. Urogenital and gastrointestinal tracts revealed no changes. Examination of the head was not permitted.

DISCUSSION

This case is of interest for two reasons: first, to record the pathologic findings in a case of lipoid nephrosis in a state of remission; and second, to add to the limited series recorded^{1, 2} one additional case of fulminant viral hepatitis in a child as a result of plasma administration (homologous serum jaundice).

The first problem presented by this case is the morphologically unimpressive renal lesion which obviously must be related to the clinical picture of the lipoid nephrosis. It appears clear that what has been originally lumped together under the name "nephrosis" by Volhard and Fahr should be subdivided into two conditions. One reveals primary involvement of the tubular apparatus, often on the basis of an intoxication, such as with mercury. It is best called toxic or necrotizing nephrosis and characteristically is associated with functional impairment of the tubular apparatus. Uremia and hypertension are the usual findings. The second is characterized by excessive albuminuria, hypoalbuminemia, hypercholesterolemia, and lipid deposition in the renal tissue. This type is not necessarily associated with uremia, hypertension, and impaired renal function. Functionally, the basic defect appears to be a pathologically

increased permeability of the glomerular loops to both serum proteins and lipids. This is associated with the morphologic picture of a thickened basement membrane of the glomerular loops. The anatomical changes of the tubules, namely, fatty metamorphosis and albuminoid swelling, have no functional significance.

The nephrotic syndrome as a clinical entity has been exhaustively studied^{9, 14, 19} and its various clinical and biochemical features are well known. Whether this distinctive clinical syndrome is the manifestation of a stage in the course of a glomerulonephritis⁵ or of several fundamentally different diseases¹¹⁻¹³ is a controversial subject. There is no doubt that some nephrotic patients show unquestionable evidence of chronic glomerulonephritis^{20, 21} and may die in uremia, and that in these cases the nephrotic syndrome is a stage in the course of the glomerulonephritis. It is also well known that others exhibiting the nephrotic syndrome do not show the usual findings of nephritis,¹¹ the hematuria, azotemia, and hypertension. These latter are the cases that are clinically called pure lipoid nephrosis and it is in this group that recoveries are most frequently reported, particularly since the advent of antibiotics and chemotherapy.

On prolonged observation it has been found that patients exhibiting the nephrotic syndrome generally show bouts of hematuria and often have transitory episodes of hypertension and azotemia, making it increasingly difficult to separate from the syndrome the so-called pure lipoid nephrosis. It has also been observed that many patients with supposed "lipoid nephrosis" later show pronounced nephritic symptoms and die in uremia. It has been stated that these patients develop a secondary, superimposed nephritis.²⁷ It seems more logical to postulate that there is but one underlying disease⁸ and that lipoid nephrosis is an early, perhaps reversible, stage of a chronic glomerulonephritis. This is essentially the conclusion of Ellis, Evans, and Wilson^{10, 22} who, in their new and valuable classification, consider it a stage of hydremic or Type II nephritis. In the few autopsy records available of patients dying during the "pure" stage of lipoid nephrosis, glomerular changes are usually reported^{11, 14-18} and only occasionally have they been missed.^{11, 12, 11, 16, 17}

The presented case offers the opportunity to observe a quiescent case. During the fully developed stage (up to two months before death), there were the typical findings of the "pure" nephrotic syndrome without hematuria, azotemia, hypertension, or impairment of renal function. Several months later, after a death not related to renal disease, few scattered adhesions between glomerular loops and some focal thickening of the basement membrane are found. Both can be considered a residue of a preceding glomerular inflammation. The small fat droplets on the base of the epithelial cells of the proximal convoluted tubules are typically found in the fulminant form of infectious hepatitis⁴ and thus not related to the previous renal condition. In general, the findings in this case support the viewpoints of those who claim the nephrotic syndrome is a stage in the evolution of glomerulonephritis, a stage in which pathologically increased permeability of the glomerular loops for proteins is the predominating feature.

The second problem presented by this case is that of homologous serum jaundice, or hepatitis, which has come into prominence in recent years with the popular use of pooled plasma or serum.^{23, 24} While attention has been focused on the disease chiefly by its high incidence in military personnel, the extensive use of these biological products on infants and children has also made this disease a pediatric problem.¹ However, reports on homologous serum hepatitis in infants and children are still rather meager, and most of the reported cases are very severe or fatal.^{25, 26} The long incubation period often makes it difficult to relate the acute illness to the previous administration of plasma or serum. The characteristic clinical syndrome is that of acute onset, fulminating course, with vomiting, jaundice, coma, and shock. The presented case ran the typical fulminating course.

Histologically, the liver presents all the characteristics of the condition which previously has been called acute yellow atrophy, and which Lucké and Mallory⁴ recently described as a fulminant stage of epidemic hepatitis. The main characteristics are the rapid, almost explosive death of the epithelial cells simultaneously with a marked mesenchymal reaction, characterized by intra-lobular and portal infiltration by histiocytic elements. Histologic examination on an extensive material on adults has revealed characteristic differences between the form of acute hepatic necrosis, described by Lucké³ and Lucké and Mallory,⁴ which is caused by viral infection, and a second form with slow cell death which is usually produced by hepatotoxic substances. Such a division into viral and toxic forms is also possible in children⁶ and the presented case is an example of the viral form. The viral form, developing as a result of administration of plasma or material contaminated with plasma, is usually more severe than the naturally occurring type, and has a long incubation period ranging from two to eight months, in the present case being from 93 to 136 days. The incubation period cannot be more exactly determined since it is obviously unknown as to which plasma sample was contaminated. Fatalities from this condition are being reported with increasing frequency, and suggest caution in the use of plasma in children as well as in adults.

SUMMARY

The clinical and pathologic findings on a 3-year-old girl, who developed fatal fulminant infectious hepatitis from the administration of plasma as treatment for a clinically "pure" lipoid nephrosis, are described. The plasma was administered four and one-half months before death, and the remission occurred two months before death. The only significant histologic renal alterations were scattered adhesions of the glomerular loops with focal thickening of the basement membrane.

REFERENCES

1. Sidbury, J. B., and Hall, R. S.: Homologous Serum Hepatitis, *J. PEDIAT.* 32: 420, 1948.
2. Wood, D. A., and Black, M. G.: Further Notes on the Pathology of Epidemic Hepatitis and Homologous Serum Jaundice, *Am. J. Clin. Path.* 16: 746, 1946.
3. Lucké, B.: The Pathology of Fatal Epidemic Hepatitis, *Am. J. Path.* 20: 471, 1944.
4. Lucké, B., and Mallory, T.: The Fulminant Form of Epidemic Hepatitis, *Am. J. Path.* 22: 867, 1946.

5. Popper, H., and Franklin, M.: Viral Versus Toxic Hepatic Necrosis, *Arch. Path.* 46: 338, 1948.
6. Popper, H., and Volk, B. W.: Hepatitis in Children, Anniversary Volume in Honor of Dr. Abraham Levinson, New York, 1949, Froben Press, Inc., chap. 23.
7. Neefe, J.: Hepatitis, *Am. J. Med.* 4: 285, 1948.
8. Bell, E. T.: Renal Diseases, ed. 5, Philadelphia, 1947, Lea & Febiger, p. 140.
9. Bradley, S. E., and Tyson, L. J.: The "Nephrotic Syndrome," *New England J. Med.* 238: 223, 1948.
10. Ellis, Evans, and Wilson, cited by Hadfield, Geoffrey, and Garrod, Lawrence P.: Recent Advances in Pathology, ed. 5, Philadelphia, 1947, The Blakiston Company, p. 278.
11. Leiter, L.: Nephrosis, *Medicine* 10: 135, 1931.
12. Murphy, F. D., Warfield, L. M., and Grill, J., and Annis, E. R.: Lipoid Nephrosis; Study of Nine Patients With Special Reference to Those Observed Over Long Periods, *Arch. Int. Med.* 62: 355, 1938.
13. Farr, L. E.: Nephrosis, Recent Advances in Internal Medicine, Vol. I, New York, 1942, Interscience Publishers, Inc., p. 223.
14. Block, W. M., Jackson, L. R., Stearns, G., and Butsch, M. P.: Lipoid Nephrosis: Clinical and Biochemical Studies of 40 Children with Ten Necropsies, *Pediatrics* 1: 733, 1948.
15. Moschowitz, E.: The Validity of Nephrosis as a Morphological Concept, *J. Mt. Sinai Hosp.* 8: 787, 1942.
16. Wolbach, S. B., and Blackfan, D.: Clinical and Pathological Studies on So-called Tubular Nephritis (Nephrosis), *Am. J. Med. Sc.* 180: 453, 1930.
17. Schwartz, H., Kohn, J. L., and Weiner, S. B.: Lipoid Nephrosis, Observations Over a Period of Twenty Years, *Am. J. Dis. Child.* 65: 355, 1943.
18. Blackman, S. S.: Pneumococcal Lipoid Nephrosis and the Relation Between Nephrosis and Nephritis. I. Clinical and Anatomical Studies, *Bull. Johns Hopkins Hosp.* 65: 1, 1934.
19. Routh, J. I., Knapp, E. L., and Kobayashi, C. K.: Electrophoretic Studies of Plasma and Urinary Proteins in Children With Lipoid Nephrosis, *J. PEDIAT.* 33: 688, 1948.
20. Christian, H. A.: Bright's Disease, New York, 1948, Oxford University Press, p. 140.
21. Addis, T.: Glomerular Nephritis, Diagnosis and Treatment, New York, 1948, The Macmillan Company, p. 206.
22. Ellis, A.: Natural History of Bright's Disease, *Lancet* 1: 34, 72, 1942.
23. Scheinberg, H., Kinney, T. D., and Janeway, C. A.: Homologous Serum Jaundice, *J. A. M. A.* 134: 841, 1947.
24. Brightman, I. J., and Korns, R. F.: Homologous Serum Jaundice in Recipients of Pooled Plasma, *J. A. M. A.* 135: 268, 1947.
25. Schmidt, E. C. II., and Lee, C. H.: Fatal Serum Hepatitis in a Young Infant, *J. PEDIAT.* 34: 226, 1949.
26. Bruyn, H. B.: Homologous Serum Hepatitis Following Transfusion in an Infant, *J. PEDIAT.* 31: 60, 1947.
27. Lyttle, J. D., and Goetttsch, E.: Brennemann's Practice of Pediatrics, Vol. III, Hagerstown, 1948, W. F. Prior Co., chapt. 28, p. 13.

THE CEPHALIN-CHOLESTEROL FLOCCULATION TEST IN INFANTS AND CHILDREN

WITH EVALUATION OF A MICROTECHNIQUE

C. W. BIEDEL, M.D.
BREMERTON, WASH.

THE need for pediatric standards for the cephalin-cholesterol flocculation test has been stated by current authors. When Krautman introduced his microtechnique utilizing capillary blood,¹ he offered a procedure practicable for pediatric use. It has been the purpose of this study to evaluate this microtechnique further and to determine the normal reactions for pediatric patients.

MATERIAL AND METHODS

The patients examined were the admissions to Children's Hospital and to the newborn nursery of the Starling-Loving Hospital, College of Medicine, Ohio State University.

In the initial phase of this study parallel tests by the technique of Hanger,² utilizing venous blood, and by the microtechnique, utilizing capillary blood, were made on all patients, including those with clinical evidence of liver disease. Patients who were examined ranged from 3 days to 15 years in age. Diagnoses included the gamut of admissions to a pediatric hospital, from orthopedic surgery to gastroenteritis.

The second phase of the study included only patients who showed no clinical evidence of liver disease. The microtechnique alone was used in the study of additional patients for this phase. In addition to the patients tested at Children's Hospital, thirty-five determinations were run on newborn infants at Starling-Loving Hospital. Of these, twenty-nine were drawn within twenty-four hours of birth.

Outlines of the two techniques follow:

Hanger Technique as Modified by Neefe and Reinhold.³—

Reagents: (1) Cephalin-cholesterol stock antigen;* (2) cephalin-cholesterol antigen emulsion; and (3) isotonic saline solution.

Technique: To 0.2 c.c. of fresh serum, add 3.8 c.c. of normal saline, and 1 c.c. of cephalin-cholesterol antigen emulsion. Mix gently and incubate at room temperature in a dark cabinet for forty-eight hours. Read at twenty-four and forty-eight hours.

Microtechnique of Krautman as Modified by Us.—

Reagents: (1) Cephalin-cholesterol stock antigen: add 5 c.c. of reagent ethyl ether to one unit of Difeo antigen. This will keep indefinitely if refrigerated at 0° C.

(2) Cephalin-cholesterol antigen emulsion: the standard technique of preparation of the antigen emulsion as outlined by Hanger was used for both techniques. To 35 c.c. of freshly distilled water heated to 65° to 70° C., add dropwise with stirring 1 c.c. of the stock antigen suspension. Evaporate at 85° to 95° C.

From the Children's Hospital, Columbus, Ohio, Department of Pediatrics, College of Medicine, Ohio State University.

*Cephalin-cholesterol antigen was obtained from the Difeo Laboratories, Inc.

until the volume is reduced to about 30 c.c. Cool; make to exactly 30 c.c. with freshly distilled water. This antigen emulsion is stable for about one week if kept in a dark cabinet at room temperature.

(3) Alkaline normal saline solution: in a 500 c.c. volumetric flask, dissolve 4.25 Gm. of sodium chloride (C.P.) in 150 c.c. of distilled water. Add 17 c.c. of N/50 sodium hydroxide and make to volume with distilled water. This solution is stable, especially if refrigerated.

Technique: Place 1 c.c. of alkaline saline solution in a plain 15 c.c. centrifuge tube. Draw exactly 20 c.mm. of capillary blood, blow blood from pipette into the saline, and mix by shaking. The finger and the lancet must be free of alcohol. As soon as possible centrifuge the suspension to precipitate the red cells and decant the supernatant solution into another centrifuge tube. To this supernatant add 0.1 c.c. of the antigen emulsion, mix gently without inversion, stopper with a cotton plug, and incubate at room temperature in a dark cabinet. Read at twenty-four and forty-eight hours.

Interpretation: In a completely negative reaction the emulsion remains in homogeneous suspension. A moderate flocculation which remains in suspension or settles out with little clearing of the supernatant solution indicates a trace or one-plus reaction dependent upon the amount of flocculation. Marked flocculation with settling, associated with partial clearing of the supernatant solution, indicates a two-plus to three-plus reaction. A water-clear supernatant solution indicates a four-plus reaction.

A wide variation in the subjective interpretation of the turbidity of the supernatant fluid was observed with different technicians. To decrease this variation a turbidometric adaptation was introduced.

Standards are prepared by adding 0.2 c.c. of the antigen emulsion to 2 c.c. of alkaline saline solution; 1 c.c. of this is removed, and twofold, fourfold, and eightfold dilutions are prepared. These dilution standards correspond to the minimum turbidity of the supernatant fluids from negative, one-plus, two-plus, and three-plus reactions, respectively. Clearer supernatant fluid indicates a four-plus reaction. Fresh standards must be prepared with each series of tests.

In reading the determinations the amount of flocculation is noted at the end of forty-eight hours. The flocculant material is then precipitated by high-speed centrifugation for five minutes and the supernatant emulsion decanted. In our practice, comparison of the turbidity of the test sample and the standards was made with a Coleman Spectrophotometer, model No. 11, using a PC-4 filter at 445 mu. For this instrument it was necessary to dilute samples and standards to 6 c.c. for reading. The dilution factor which is necessary will vary with the comparator which is used for the measurement of turbidity.

Although this adaptation was used principally with the microtechnique, it is equally applicable to the standard cephalin-cholesterol flocculation procedure.

RESULTS

The first phase was the evaluation of the microtechnique by parallel testing and an analysis of the problems encountered. The second phase was the collection of normal values.

Evaluation of the Microtechnique.—At the present time it is believed that the cephalin-cholesterol flocculation is dependent upon a quantitative and qualitative variation in the albumin fraction in relation to the globulin fraction of the serum.^{4,5} Because whole blood is drawn for this determination, it was suggested that variations in hematocrit would alter the results by varying the absolute quantity of serum used for the test. Therefore, simultaneous determinations

using 10, 15, 20, 25, and 30 c.mm. of whole blood were run on six patients whose hemoglobins varied from 7.8 to 11.7 Gm. (Table I). Variation at either extreme occurred in two-thirds of the cases but showed no consistent pattern of deviation. Five additional patients under treatment for megaloblastic anemia with hematocrits of 24 to 36 per cent showed no abnormal results.

TABLE I. DILUTION FACTOR IN CEPHALIN-CHOLESTEROL FLOCCULATION TEST

CASE	HEMO-GLOBIN (GM.)	CUBIC MILLIMETERS OF WHOLE BLOOD USED IN TEST				
		10	15	20	25	30
		REACTIONS				
118	11.7	1+	1+	1+	1+	1+
119	7.8	2+	1+	1+	1+	1+
125	11.5	-	2+	2+	2+	1+
172	8.1	1+	2+	2+	2+	2+
175	9.7	1+	1+	1+	1+	1+
176	11.7	1+	±	±	±	1+

Variation in the sensitivity of the antigen emulsion with age has been emphasized by many authors. Results of tests on 201 normal sera are presented in Table II. Statistically there is significant correlation between the increasing age of the antigen and the per cent of completely negative reactions. There is no significant increase in plus-minus reactions, and one-plus reactions show a significant degree of variation on one occasion only. There is no significant increase in the number of abnormal responses obtained with increasing age of the antigen emulsion.

TABLE II. RELATION OF AGE OF ANTIGEN TO ANTIGEN SENSITIVITY

Age of antigen (in days)	1	2	3	4	5	6
No. cases studied	50	46	48	22	27	8
Reactions (per cent of cases)						
Negative	26.0	10.9	4.2	0.0	3.7	0.0
Plus-minus	30.0	39.1	14.6	31.8	29.6	50.0
One plus	42.0	39.1	75.0	59.2	59.3	50.0
Two plus	2.0	10.9	6.2	4.5	7.4	0.0
Three plus	0.0	0.0	0.0	4.5	0.0	0.0

Delay in the separation of the red cells from the supernatant diluted serum will result in false positive reactions if that delay is too great (five to six hours). No instance of this is known to have occurred in the present series although it is our impression that the absence of negative reactions among the newborn infants may be due to such a delay. Due to geographical factors a delay of from one to two hours was invariably encountered before separation of the supernatant fluid could be accomplished in this series of tests.

Difficulty in interpretation of the minor changes of turbidity associated with one-plus and two-plus reactions was noted with both tests. For this reason, the turbidometric technique previously described was adopted.

Occasional reactions were seen which interfered with interpretation. The more frequent type resembled a serum clot surrounded by clear fluid. The clot involved the emulsion and showed no evidence of flocculation. This occurred in 8 of 288 determinations (2.8 per cent). The other type revealed precipitation of a part of the emulsion on the walls of the centrifuge tube without true floccu-

lation or clearing of the supernatant fluid. This occurred in three of 288 tests (1.0 per cent). When reactions of these types occur, the determination must be rerun.

Comparison of Microtechnique With Modified Hanger Technique.—A total of 111 parallel determinations were made. Tests in which both techniques gave results of zero to one plus, or from two plus to three plus, were considered to be in satisfactory agreement. On this basis 104 tests (94.5 per cent) correlated (Table III). In six of the seven cases which failed to agree, the microtechnique gave a more positive result. In the remaining case, the Hanger technique, using serum forty-eight hours old, was more positive. A summary of the six patients involved, including diagnoses and the results of earlier or subsequent tests, is included in Table IV.

TABLE III. RESULTS OF PARALLEL TESTING BY HANGER AND BY MICROTECHNIQUES*

		HANGER TECHNIQUE								
		0	1	±	1	+	1	++	1	+++
MICRO- TECH- NIQUE	0		12	3		3				
	±		6	14		1				
	+		6	21		25		1†		
	++		1			4		9		1
	+++					1		2		1

*One hundred and eleven determinations.

†Italicized numbers indicate cases where agreement of the two tests was considered to be unsatisfactory.

TABLE IV. SUMMARY OF CASES IN WHICH STANDARD AND MICROTECHNIQUES FAILED TO AGREE

PATIENT	DIAGNOSIS	AGE	DATE	STANDARD	MICRO
P. S.	Enteritis	3 mo.	10/25	1+	2+
J. B.	Megaloblastic anemia	9 mo.	10/16	2+	1+
J. M.	Hydronephrosis	12 mo.	10/12 10/18 10/27	2+ 1+ —	3+ 2+ 1+
M. L.	Cellulitis of the leg with purpura	11 yr.	10/12 10/16 10/17	1+ 0 —	3+ 2+ 2+
M. G.	Observation for rheumatic fever	13 yr.	10/25	1+	2+
R. K.	Atresia of the bile ducts	5 mo.	10/30 11/8 11/19	2+ — 1+	2+ 2+ 2+

This degree of correlation would appear to be sufficient to accept the microcephalin-cholesterol flocculation as a valid method, especially useful in pediatric institutions. The evidence suggests that no positive reactions will be missed, although occasional false positive reactions will be encountered.

Evaluation of Results in Patients Clinically Free of Liver Disease.—Eighty-three determinations involving seventy-eight patients were done by the modified Hanger technique. The results are presented in Table V. Of the tests, only two (2.4 per cent) showed flocculation greater than one plus. One of these tests was run on serum forty-eight hours old; the other test involved a hydrocephalic patient.

Two hundred one determinations, involving 189 patients, done by the microtechnique are summarized in Table VI. Of these, twelve tests (6.0 per cent) showed greater than one-plus flocculation. Repeat determinations, when pos-

TABLE V. RESULT OF CEPHALIN-CHOLESTEROL FLOCCULATION TEST BY HANGER TECHNIQUE IN PATIENTS CLINICALLY FREE OF LIVER DISEASE*

	AGE					
	1-13 WEEKS	3-12 MONTHS	1-3 YEARS	3-6 YEARS	6-10 YEARS	OVER 10 YEARS
Reactions						
0	2	1	1	3	10	6
±	0	5	7	5	8	9
+	2	6	3	3	3	7
++	0	2	0	0	0	0

*Eighty-three determinations on seventy-eight patients.

TABLE VI. RESULTS OF CEPHALIN-CHOLESTEROL FLOCCULATION TEST BY MICRO-TECHNIQUE IN PATIENTS CLINICALLY FREE OF LIVER DISEASE*

	AGE						
	0-5 DAYS	1-13 WEEKS	3-12 MONTHS	1-3 YEARS	3-6 YEARS	6-10 YEARS	OVER 10 YEARS
Reactions							
0	0	3	5	1	2	8	3
±	10	7	9	8	7	8	8
+	23	11	17	19	7	10	23
++	2	0	3	1	1	1	3
+++	0	1	6	0	0	0	0

*201 determinations on 189 patients.

sible, were within normal limits in all cases. These false positive reactions occurred in a wide variety of conditions (Table VII) without apparent explanation.

On the basis of these determinations, the previously accepted standard for adults for the cephalin-cholesterol flocculation test (normal equals a negative to one-plus reaction) may be extended to include infants and children of all age levels.

TABLE VII. CASES SHOWING FALSE POSITIVE REACTIONS

Newborn infant	2
Convalescent influenzal meningitis	2
Hydrocephalus	1
Convalescent poliomyelitis	1
Rheumatic fever, subacute	1
Birth injury	1
Postoperative cases	4
Herniorrhaphy	1
Fracture-dislocation of elbow	1
Tumor of hand, nonmalignant	1
Tendon transplant	1
(Tests done within seventy-two hours of anesthesia)	

CONCLUSIONS

A microtechnique for the cephalin-cholesterol flocculation test utilizing capillary blood is presented in detail.

One hundred eleven parallel determinations revealed 94.5 per cent agreement of the microtechnique with the standard Hanger technique; the microtechnique appeared more sensitive.

Analysis of 284 determinations on pediatric patients with no evidence of liver disease revealed 97.6 per cent of the Hanger reactions and 94.0 per cent of the micro reactions to be one plus or less.

REFERENCES

1. Krautman, B.: Micro Cephalin-Cholesterol Flocculation Test on Blood From Finger, Am. J. Clin. Path. Tech. Section 10: 126, 1946.
2. Hanger, F. M.: Serological Differentiation of Obstructive From Hepatogenous Jaundice by Flocculation of Cephalin-Cholesterol Emulsions, J. Clin. Investigation 18: 261, 1939.
3. Neefe, J. R., and Reinhold, J. G.: Photosensitivity as a Cause of Falsely Positive Cephalin-Cholesterol Flocculation Tests, Science 100: 83, 1944.
4. Guttman, S. A., and Others: Significance of Cephalin-Cholesterol Flocculation Test in Malarial Fever, J. Clin. Investigation 24: 296, 1945.
5. Moore, D. B., Pierson, P. S., Hanger, F. M., and Moore, D. H.: Mechanism of the Positive Cephalin-Cholesterol Flocculation Reaction in Hepatitis, J. Clin. Investigation 24: 292, 1945.

A METHOD FOR THE DETERMINATION OF NITRATES IN MILK AND INFANT FORMULA

GORDON M. KRUEGER, M.A.

GREENVILLE, ILL.

COMLY,¹ in his report on two case histories of infants having methemoglobinemia, gives a very interesting and thorough history of this problem of high nitrate well water and how it affects the hemoglobin of the blood to cause methemoglobinemia. Comly stated that in trying to analyze the milk formula for its nitrate content, caramelization occurred which prevented completion of the analysis.

The phenoldisulfonic acid method² is the usual method of analysis for nitrates; however, in searching through the literature, the method of Noll³ was noted. This method employed the brucine reagent⁴ and had the advantages of simplicity, color stability, few interfering ions (except possible organic material), a sensitivity of 0.3 part per million and an accuracy of 0.5 part per million nitrate in the range of nitrate concentrations from 0 to 50 parts per million as NO_3^- . Noll adapted a Klett-Summerson photoelectric photometer for nitrate analysis. This method was chosen for use in this investigation.

Since caramelization occurs in analysis of infant formula for nitrate content, it was necessary to remove the sugar (milk sugar and the added sugar from formula) before proceeding with the analysis. The action of acid and heat on the sugar present naturally results in the production of a dark discoloration prohibiting further analysis. As a result, the removal of sugar becomes very important and was accomplished by adapting a procedure similar to that used by Barker and Summerson.⁵

STANDARDIZATION AND RESULTS

Using the method of Noll, a standard nitrate curve was outlined using solutions of known nitrate values. From this calibrated curve the data tabulated in Table I were obtained. A Klett-Summerson photoelectric colorimeter and a blue filter with a range of 400 to 465 $\text{m}\mu$ were employed. A water blank was used to adjust the instrument to zero.

All results in this work are expressed in terms of nitrate nitrogen. A conversion factor of 4.4 was used to change nitrate values to nitrate nitrogen.

When necessary, the original water sample was diluted with distilled water prior to color development.

In order to analyze infant formula or milk samples for nitrate, the sugar was removed in order to prevent caramelization. As stated previously, this was accomplished by the following adaption from the method of Barker and Summerson.

From the Research Laboratories, Pet Milk Company.

To a 50 ml. centrifuge tube the following materials were added in the order listed:

- 3.5 ml. infant formula (or milk)
- 3.5 ml. cupric sulfate (20 per cent)
- 24.0 ml. distilled water
- 3.5 Gm. calcium hydroxide.

The tube was stoppered, thoroughly shaken, and let stand for thirty minutes. After standing, the tube was centrifuged until a clear, supernatent layer was obtained. If at all turbid, this layer was pipetted off and filtered (Whatman No. 42). Five milliliter portions were placed in 50 ml. beakers and analyzed for nitrate using the brucine reagent. Another 5 ml. sample was run simultaneously as a blank (no brucine added). Failure to remove sufficient sugar to prevent caramelization would be shown by discoloration in the blank.

TABLE I. NITRATE RECOVERIES USING THE BRUCINE REAGENT

NO.	SAMPLE	NITRATE NITROGEN (PPM)		
		ADDED	FOUND	% RECOVERY
1	Distilled water standard	100	100	100
2	Distilled water standard	100	97.7	97.7
3	Distilled water standard	500	500	100
4	Distilled water standard	500	488.6	97.7
5	Regular evaporated milk	0	1.25	—
6	Regular evaporated milk	70	60.2	86.0
7	Infant formula (not sterilized)	70	60.8	86.8
8	Infant formula (sterilized)	70	60.8	86.8
9	Infant formula (sterilized)	70	61.9	88.4
10	Infant formula (sterilized)	350	336.0	96.0

From Table I it is readily seen that better recoveries were obtained from the regular standards than from the milk samples. All of the samples were carried through the sugar-removing procedure. It is difficult to explain the lower recoveries in the milk samples. Dilution of the filtrate (after centrifuging) and precipitation of excess calcium prior to color development was tried without increasing the recovery percentage. However, even with an 87 per cent recovery, it is felt that this method is still of value in that it permits at least a semiquantitative measurement of nitrate. As a result, by employing this procedure for eliminating the effect of sugar, an estimation can be made as to the nitrate content of milk formula suspected of being responsible for methemoglobinemia.

SUMMARY

A semiquantitative method is outlined whereby milk and infant formula can be analyzed for nitrate without interference by caramelization from lactose or the added sugar in the formula.

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REFERENCES

1. Comly, H. H.: Cyanosis in Infants Caused by Nitrates in Well Water, *J. A. M. A.* 129: 112-116, 1945.
2. Standard Methods for the Examination of Water and Sewage, ed. 9, New York, 1946, American Public Health Association.
3. Noll, Charles A.: Determination of Nitrate in Boiler Water by Brucine Reagent, *Indust. & Engin. Chem. (Anal. Ed.)* 17: 726, 1945.
4. Snell, F. D., and Snell, C. T.: "Colorimetric Methods of Analysis," Vol. 1, ed. 2, New York, 1936, D. Van Nostrand Co., p. 635.
5. Barker, S. B., and Summerson, William H.: The Colorimetric Determination of Lactic Acid in Biological Material, *J. Bio. Chem.* 138: 535, 1941.

A METHOD FOR THE REMOVAL OF NITRATES FROM WATER PRIOR TO USE IN INFANT FORMULA

GORDON M. KRUEGER, M.A.
GREENVILLE, ILL.

INFANT methemoglobinemia due to high nitrate waters is an important problem, especially in certain rural areas. One of the earliest reports of numerous cases of infants having this disease was in 1945 by Comly¹ in Iowa. Ferrant,² and Faucett and Miller³ also reported methemoglobinemia in infants who had ingested milk diluted with well water having a high nitrate content. In 1947, thirty-three cases were reported in Illinois with five fatalities.⁴ No doubt many more similar cases that have not been publicized have occurred elsewhere, especially since it is known that high nitrate waters have been found in at least ten of our states and three foreign countries.

The nitrate nitrogen content of the water used in most of these reported cases ranged from 25 to 300 parts per million.⁵ In Comly's report considerable bacterial contamination was noted in the water used, as well as a high nitrate content. However, Johnson⁶ and his workers found that a high concentration of nitrate nitrogen can occur in water in which no coliform organisms are demonstrable. Weart⁷ states that no correlation was found between the presence of large amounts of nitrate and the sanitary quality of the water. As a result, it appears that there is not anything definitely predictable as to bacterial content and high nitrate content of the waters in question.

Since 1945 there has been more and more attention given this particular infant disease. It is generally noted in rural areas where the water supply is from a shallow well which has been dug rather than drilled. To change the water supply is not often convenient due to adverse weather conditions, transportation problems, or the financial status of the family involved. As a result, it would be advantageous for all concerned if the family doctor had a method for removal of, or at least a safe reduction of, the nitrate content of the water. The doctor could demonstrate the effect of the treatment, and thereafter the family could follow his simple instructions in making routine preparations of low nitrate water for use in the infant formula.

It was with this thought in mind that the following experimental work was conducted and the results given in this report.

The preceding report covered the analytical approach on this problem of nitrate removal from well water to be used by infants, either as drinking water or in milk formula.*

EXPERIMENTAL RESULTS

The thought of trying some ion exchange material seemed the most practical approach in trying to reduce the nitrate content of well water. Meyers,

From the Research Laboratories, Pet Milk Company.

*See page 479.

Eastes, and Meyers⁸ predicted many unique or special applications of their synthetic resins. The chemical efficiency and capacity for anion removal by these exchange resins in water purification was shown by Meyers and Eastes.⁹ Since our problem involved only the anion, NO_3^- , we obtained quantities of the anion exchange resins, Amberlite IR-4B and IRA-400, for this work.

The method of Bray¹⁰ was used for a rapid, simple estimation of the nitrate content of water. In this test, a pink to reddish color, which is proportional to the amount of nitrate present, develops.

INITIAL TEST FOR NITRATE REMOVAL

One hundred milliliters of a standard solution (100 parts per million nitrate nitrogen) were mixed for ten minutes with 5 Gm. of the IRA-400 resin. After this treatment, a sample of this water indicated removal of nitrates to approximately 10 parts per million (a slight pink color). The untreated control gave a dark brownish-red color showing excessive nitrates present. This simple test indicated that it was possible to reduce the nitrate content to a safe level and stimulated a series of experiments to determine the following: (1) the minimum exposure time needed to remove nitrates; and (2) the minimum amount of resin for maximum removal of nitrates.

A. Batch Method for Removal of Nitrate.—

Series I. IRA-400: One hundred milliliters of nitrate nitrogen standard (100 parts per million) were stirred fifteen minutes with different amounts of the resin with the following results:

- No. 1 1 Gm. resin, most red color.
- No. 2 3 Gm. resin, less color than 1, more than 3.
- No. 3 5 Gm. resin, least color (a slight pink).

Series II. IRA-400: One hundred milliliters of the 100 parts per million nitrate nitrogen standard plus 5 Gm. resin were given different stirring times to give the following results:

- | | | |
|-------|------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| No. 1 | 1 minute | } All four stirring times gave a similar color (sl. pink), indicating that only a short exposure time is needed to effect removal of nitrate. |
| No. 2 | 5 minutes | |
| No. 3 | 15 minutes | |
| No. 4 | 25 minutes | |

A 10 parts per million nitrate nitrogen standard gave a similar pink color as obtained in Series II.

Series III. IRA-400 and IR-4B: One liter of tap water was placed in a 2 liter screw top jar. Tests for nitrate were made after various shaking times. The results shown in Table I.

These results (Table I) indicate that the most economical amount of resin to give the maximum decrease in nitrates is in 30 Gm. per liter of tap water (100 parts per million nitrate nitrogen added) with a minimum shaking time of three minutes. The resin IRA-400 showed a decided advantage over IR-4B in the speed of nitrate adsorption.

This preliminary work is further supported by the results obtained and shown in Table II.

TABLE I. EFFECT OF VARYING RESIN AND EXPOSURE TIME

NO.	SAMPLE	RESIN (GM.)	TIME SHAKEN		
			1 MIN.	3 MIN.	6 MIN.
I	Tap water	0	Red	-----	-----
	Tap water	10 (IRA-400)	Light red	-----	-----
II	Tap water with 100 ppm nitrate nitrogen	10 (IRA-400)	Brownish red	Brownish red	Brownish red
	Tap water	30 (IRA-400)	Pink	-----	-----
III	Tap water with 100 ppm nitrate nitrogen	30 (IRA-400)	Lighter than in I	Light red	Light red
	Tap water	30 (IR-4B)	Darker red than in I or II	-----	-----
	Tap water with 100 ppm nitrate nitrogen	30 (IR-4B)	Brownish red, similar to I	-----	-----

TABLE II. EFFECT OF RESIN ON NITRATE CONTENT AS SHOWN BY BRUCINE REAGENT

NO.	SAMPLE	TREATMENT	NITRATE NITROGEN (PPM)	
			COLOE READ	(PPM)
1	Tap water (1 L.)*	None	160	9.6
2	Tap water (1 L.)	30 Gm. IRA-400 for 3 minutes	127	1.4
3	Tap water (1 L.)* 100 ppm nitrate nitrogen	None	330	106.8
4	Tap water (1 L.)* 100 ppm nitrate nitrogen	30 Gm. IRA-400 for 3 minutes	138	7.9

*A 1-5 dilution of sample made prior to color development.

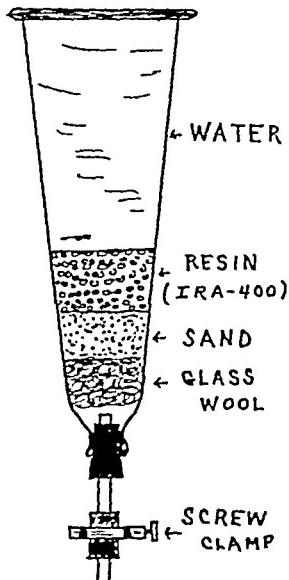


Fig. 1.—Nitrate exchange column.

B. Exchange Column Removal of Nitrate.—A very simple ion exchange column was made as shown in Fig. 1. About 22 cubic inches of the anion exchange resin were used to remove the nitrate.

One liter volumes of standard nitrate nitrogen water (100 parts per million) were poured in the top and permitted to stand one minute before draining at such a rate as to make a total exposure time of ten minutes. Five milliliter aliquots of each treated sample were analyzed for residual nitrate by the method of Noll.¹¹ The above procedure was repeated with fresh untreated portions until the residual nitrate nitrogen approached the safe limit of 10 parts per million nitrate nitrogen.¹²

The results obtained in this experimental column treatment are shown in the respective curves in Fig. 2. Tap water and distilled water were used.

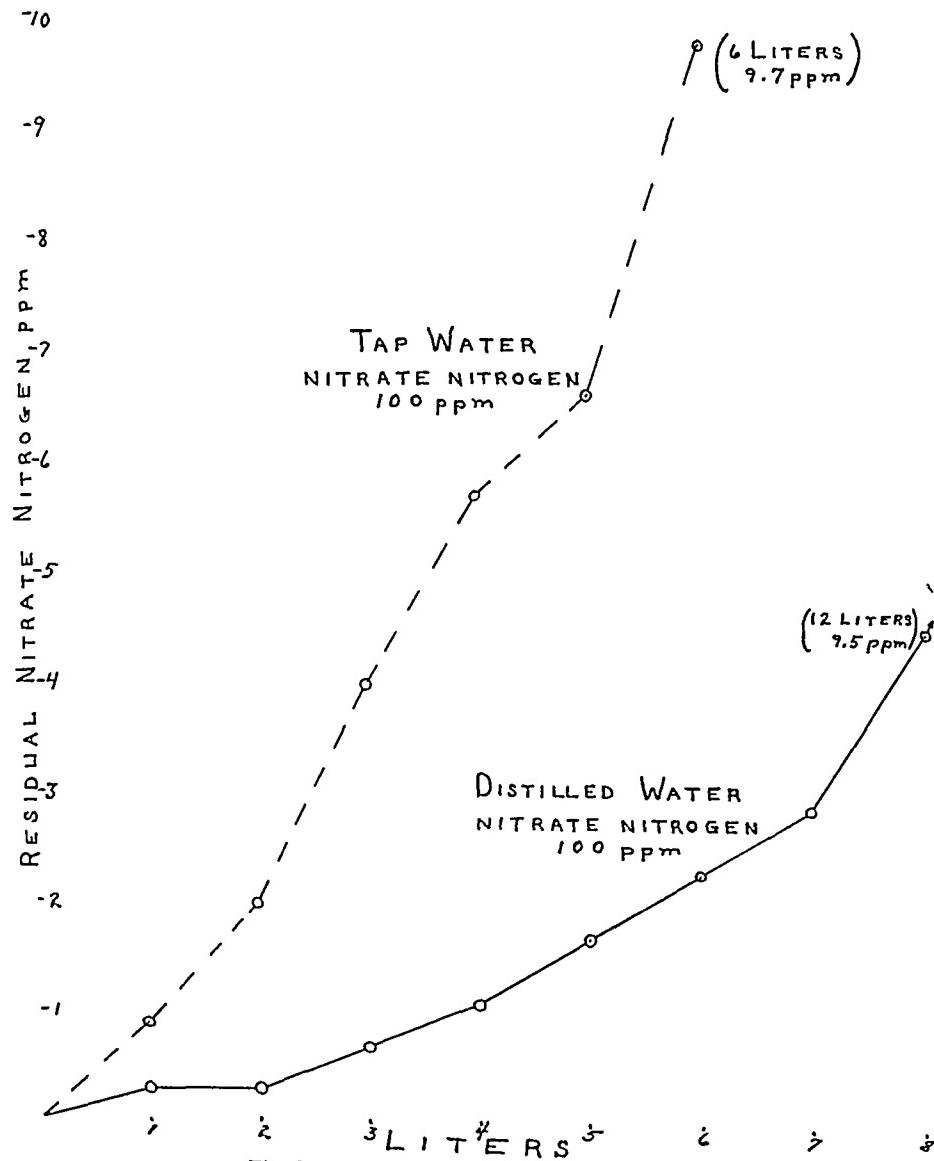


Fig. 2.—Exchange column removal of nitrate.

A new resin bed was prepared for use with each type of water. A maximum of 6 L. tap water (100 parts per million nitrate nitrogen) and 12 L. distilled water (100 parts per million nitrate nitrogen) were treated by this method.

The tap water used in this ion exchange column had a hardness of 34 grains and about 600 parts per million total solids. The effect on pH was followed in the tap water series with little change noted. The tap water had an initial pH of 7.25 and 7.05 for the first liter. A maximum pH of 7.65 was obtained in the fifth liter and a slight decrease in the last (sixth) liter to be treated, pH 7.4.

DISCUSSION

The method of nitrate removal presented is another application of ion exchange which is used so extensively in water purification. The amount of resin needed is not very great; however, a cost estimate for this treatment is uncertain at this time, since production of this resin (IRA-400) is being shifted from research to industrial quantities.¹³ The increased production should make this simple treatment even more economical.

The batch method would be the easiest and most simple for the family doctor to demonstrate in a rural area. The doctor could supply the needed resin and make the initial tests for nitrate removal. A large fruit jar with a screw top would suffice as the agitating container. A clean cloth (cheese cloth) tied or held over the jar top would retain the resin while pouring the treated water into a container. Small volumes of low nitrate water could be prepared quickly by this very simple treatment.

The column method, once set up, would, perhaps, be the most convenient and economical for preparing large volumes of low nitrate well water directly in a rural area. The exact volume which could be treated will vary with the different characteristics of the water in question. The effect of hardness and total solids in water was shown by the different volumes of tap water and distilled water which could be treated, even though each contained the same amount of added nitrate.

It would be advantageous to use a simple confirmatory test (Bray's) for the degree of nitrates present prior to treatment or actual usage of the treated water in formula preparation. In order to avoid having sodium hydroxide around infants or infant food preparations, it would not be suggested that one attempt regeneration of the material.

It is important to note that this resin treatment, while reducing the nitrate content, does not reduce any possible bacterial contamination. Therefore, the treated water should be given the heat treatment as directed in the preparation of the respective milk formula.

SUMMARY

Experimental work was conducted and data presented showing it practical and possible to reduce the nitrate content of well water to a safe level by the use of a rapid anion exchange resin either in a batch or column operation.

The author wishes to thank the officials of the Pet Milk Company, especially Dr. E. A. Louder, Technical Director, for releasing this report for publication, as well as for his supervision of the research program. The author also wishes to thank Dr. A. Z. Hodson for his advice and criticism during the course of this work and in the preparation of this paper.

REFERENCES

1. Comly, H. H.: Cyanosis in Infants Caused by Nitrates in Well Water, *J. A. M. A.* 129: 112-116, 1945.
2. Ferrant, M.: Methemoglobinemia, *J. PEDIAT.* 29: 585-592, 1946.
3. Faucett, R. L., and Miller, H. C.: Methemoglobinemia Occurring in Infants Fed Milk Diluted With Well Water of High Nitrate Content, *J. PEDIAT.* 29: 593-596, 1946.
4. Weart, J. G.: High Nitrate Waters: Their Occurrence, Source, and Significance, presented in ACS Meeting, April 19, 1948.
5. Weart, J. G.: High Nitrate Waters: Their Occurrence, Source and Significance, presented in ACS Meeting, April 19, 1948.
6. Johnson, G., Kurz, A., Cerny, J., Anderson, A., and Matlack, G.: Nitrate Levels in Water From Rural Iowa Wells, *J. Iowa State Med. Soc.*, January, 1946.
7. Weart, J. G.: High Nitrate Waters: Their Occurrence, Source and Significance, presented in ACS Meeting, April 19, 1948.
8. Meyers, R. J., Eastes, J. W., and Meyers, F. J.: Synthetic Resins as Exchange Adsorbents, *Ind. and Eng. Chem.* 33: 697, 1941.
9. Meyers, R. J., and Eastes, J. W.: Synthetic-Resin Ion Exchangers in Water Purification, *Ind. & Eng. Chem.* 33: 1203, 1941.
10. Weart, J. G.: High Nitrate Waters: Their Occurrence, Source and Significance, presented in ACS Meeting, April 19, 1948.
11. Noll, Charles A.: Determination of Nitrate in Boiler Water by Brucine Reagent, *Ind. and Eng. Chem. (Anal. Ed.)* 17: 726, 1945.
12. Comly, H. H.: Cyanosis in Infants Caused by Nitrates in Well Water, *J. A. M. A.* 129: 112-116, 1945.
13. Winters, J. C.: Personal communication with Mr. J. H. Wright, 1948.

Case Reports

SUBLINGUAL HEMATOMA AS AN UNUSUAL COMPLICATION OF HEMOPHILIA

HAROLD W. BISCHOFF, M.D.,* LAMESA, TEXAS, AND EDWARD W. NICKLAS, M.D.,
WASHINGTON, D. C.

THIS unusual complication of hemophilia, sublingual hematoma, occurred in a Brazilian boy 10 years of age. He is the oldest of four children. His younger brother, aged 5 years, is also a known hemophiliac and another boy who was born between the patient and his younger brother died at the age of 14 months of hemorrhage ascribed to hemophilia. The fourth child, recently born, was a female. One brother of the mother died during early childhood of hemorrhage presumably due to hemophilia. The father of the patient, a very intelligent young officer in the Brazilian Air Force, had made a very intensive study of the maternal family tree. He was able to uncover only two other hemophiliacs, the maternal uncle mentioned above, and a maternal cousin. The family tree is shown in Fig. 1.

CASE HISTORY

This 10-year-old white boy, a known hemophiliac, entered Children's Hospital on October 31 with a chief complaint of nausea and vomiting dating back to five days before hospital entry.

At onset, the vomiting was not severe but persistent. The following day the vomiting subsided and reappeared the next day. On this day there was an elevation of the temperature to 100.6° F. and mild abdominal discomfort. The patient continued in this status until the morning of his hospital entry when there was a rather marked abdominal pain and his private physician found rigidity over the right lower quadrant and some fullness in the pelvis upon rectal examination.

In discussing the history with the child, it was brought out that on the day of the onset he had fallen over another boy's foot and in so doing had struck his abdomen in the region of the symphysis. There was no history of immediate pain following the fall. No history was obtained of urinary symptoms during the duration of the present illness. Bowel habits were not unusual and there was no history of bloody or tarry stools.

The family history has been elaborated above. The past history revealed that the child had had numerous episodes of bleeding from minor traumata, all of which had necessitated repeated blood transfusions. He also had had numerous episodes of hemarthrosis which have resulted in considerable deformity and a peculiar "waddling" gait.

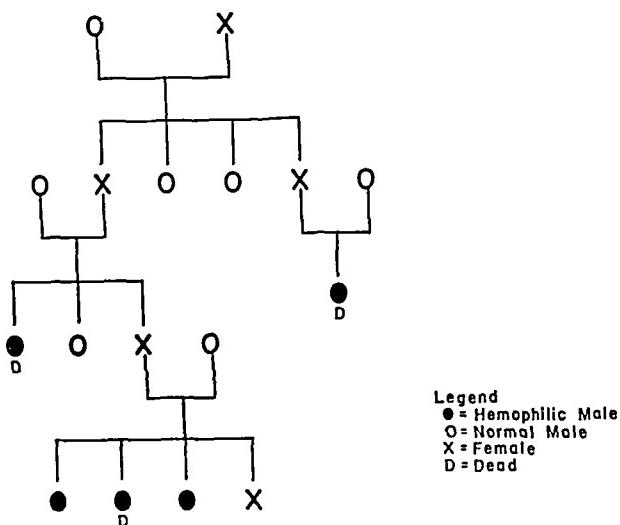
Physical examination revealed a thin white boy of stated age who lay in bed on his side with his knees drawn up. The child did not appear to be in any great pain. His face was "pinched" and "drawn" and there were deep circles under both eyes.

From the Department of Pediatrics, Children's Hospital, Washington, D. C.

*Research Fellow, National Institute of Health; Pediatric Resident, The Children's Hospital, Washington, D. C.

The remainder of the physical findings were confined to the abdomen and rectum. The abdomen was scapoidlike and moved well with respiration. There was no pain to deep palpation anywhere over the abdomen and there was no rebound tenderness. Peristalsis was normal.

The examining finger was introduced through the anal sphincter with ease. Muscle tonus was good. The prostate was not felt. There was no definite mass; however, there was a definite fullness in the pelvis anteriorly. The boy had voided approximately fifteen minutes before examination; therefore, this was not considered to represent a urine-filled bladder. The remainder of the pelvis was normal. The rectal examination was accompanied by only a moderate amount of discomfort.



Family Tree Of C. J.

Fig. 1.

A hemogram performed on entry showed 13 Gm. of hemoglobin, 5 million red blood cells, and 14,100 leucocytes with 79 per cent neutrophiles. Of the latter, 9 per cent were band forms. A urinalysis was normal. The following day the white blood count was 16,100 with 62 per cent neutrophiles. Subsequent leucocyte counts were all within normal limits as to total numbers and percentages of the component cells.

The patient was seen in surgical consultation about an hour after the initial hospital examination. At that time there was no evidence of abdominal tenderness or rigidity. Upon rectal examination the consultant was able by bimanual palpation to reach the anterior abdominal wall with the rectal finger.

Hospital Course.—The evening of hospital entry the boy complained that his tongue felt thick. Inspection of the tongue at that time did not reveal any abnormality of lingual or sublingual tissue nor of the overlying mucous membranes.

The following morning there was present beneath the tongue a large hematoma which appeared to be larger on the right side. The hematoma did not seem to be in the substance of the tongue, but rather in the sublingual loose connective tissue.

An immediate attempt was made to secure some Fraction I anti-hemophilic globulin. Since none of this was available, upon the advice of Dr. C. A. Jane-way, a transfusion of 200 c.c. of compatible blood was given within an hour after it was drawn.

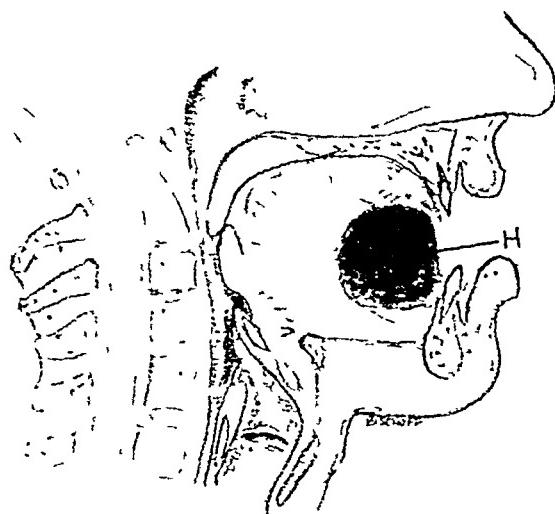


Fig. 2

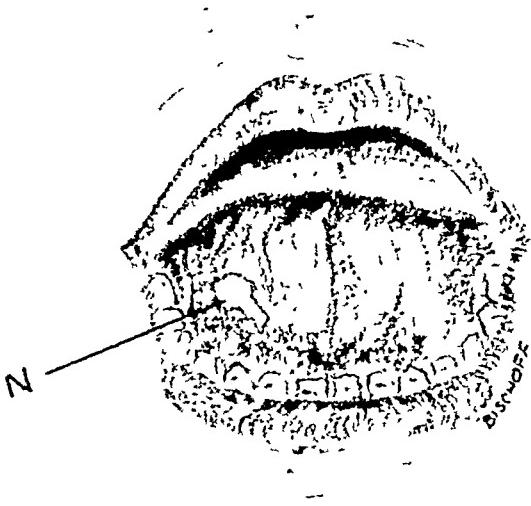


Fig. 3.

In the afternoon of the day that the hematoma appeared, it appeared larger than it did in the morning. Whereas in the morning the hematoma seemed to be limited more to the right side, in the evening it was, along with being larger,

symmetrically distributed on the two sides. By evening the boy's speech was very thick and quite difficult to understand. At this point when the child's mouth was opened the dorsum of the tongue approximated the roof of the mouth.

The following morning another transfusion of 100 c.c. of less than one-hour-old blood was given. In the afternoon of this day there seemed to be some space between the dorsum of the tongue and the hard palate. There also appeared to be more space on the left side. Inasmuch as the tongue had come down some, it was presumed that the bleeding had stopped.

The next day there was an unmistakable odor of old blood about the boy's breath. The mucous membrane of the underside of the tongue contained some areas on the right side which appeared to be becoming necrotic. The saliva which collected on the side of the mouth during examination was stained with blood. The papillae of the lateral margins of the tongue stood out in "bas relief" and the edges of the tongue had the appearance of a tissue undergoing necrobiosis. One-half strength Dobell's solution as a mouth wash and penicillin troches were prescribed at this time for their local effect.

By the next evening the tongue had almost regained its normal shape and size. It was heavily coated over its posterior portion while the anterior portion was a deep purple in color. In spite of the rather cadaverous appearance, the tongue was still freely movable. The hematoma, still present, was quite small. At this point the temperature which had previously been within normal limits, elevated to 102° F. rectally. It was thought at this point that the temperature elevation represented an infection of the hematoma and early abscess formation. Sulfadiazine, one and one-half grains per pound, was started immediately.

On the morning of his sixth hospital day, the day following the temperature elevation, the left faucial tonsil, previously normal, was enlarged and contained a number of yellow, follicular areas. This apparently explained the temperature elevation.

The child was discharged on his eighth hospital day. Upon discharge from the hospital, the tongue was of normal size. There was a minimum of discoloration over the inferior, anterolateral surface of the tongue. The mucous membrane of the sublingual area appeared to be well healed. The child's voice was again clear and comprehensible both in his native language and in English.

DISCUSSION

Since 1910 there have been eight case reports in the literature of sublingual hematoma as a complication of hemophilia.²⁻⁹ Of these eight cases, four had tracheotomies and of these four, only one survived. In the case presented at no time was there respiratory embarrassment or complete inhibition of swallowing. Although tracheotomy was at all times kept in mind as a possible eventuality, it was not necessary to resort to this procedure. Because of the fact that this child never did have difficulty with either respiration or deglutition, it was considered that the hemorrhage did not involve the muscular tissue of the tongue or the floor of the mouth. Fig. 2 shows the most probable location of the hematoma in the submucosal tissue of the sublingual area. Fig. 3 is a drawing reproducing a frontal view of the hematoma. The small area labeled "N" shows the area of necrosis.

It has been shown that the antihemophilic activity of both blood and plasma gradually disappears even though it is preserved at refrigeration temperatures.¹⁰ Accordingly, the child was given transfusions of blood within one hour of the time that it had been drawn. In this connection, it is interesting to note that both the patient and his younger brother had had episodes of bleeding a few years before which had not responded to transfusions of citrate blood, but which had responded immediately to direct blood transfusions.

SUMMARY

A case of sublingual hematoma as a complication of prolonged vomiting in a hemophiliac is presented. This increases the total number of this complication to nine since 1910.

The bleeding was controlled through the use of compatible blood administered within an hour after it had been drawn.

A brief summary of the literature is presented.

REFERENCES

1. Janeway, C. A.: Personal Communication.
2. Umbreit: Deutsche Ztschr. f. Chir. 105: 608, 1910.
3. Feliciangeli, G.: Policlinico (sez. prat.) 28: 8, 1921.
4. Dujarier, G.: Arch. Internat. de Laryng. 9: 1216, 1930.
5. Troutt, J. M.: Mil. Surgeon 69: 419, 1931.
6. Lesne, Powilewicz and Recamier: Bull. Soc. de Pediat. de Paris 19: 308, 1921.
7. Voit, K., and Plaus, T.: Ztschr. f. Hals-, Nasen- u. Ohrenh. 32: 473, 1933.
8. Endicott, C. L., Mitchell, J. H., and Qvist, G.: Brit. M. J. 2: 34, 1942.
9. Baird, K. H., and Fox, M. S.: J. PEDIAT. 23: 90, 1943.
10. Taylor, F. H. L., Lozner, E. L., Davidson, C. S., and Tagnon, H. J.: J. Clin Investigation 23: 351, 1944.

ACUTE INFECTIOUS LYMPHOCYTOSIS

PERRY D. COHN, M.D.*

PASSAIC, N. J.

INTRODUCTION

A CUTE infectious lymphocytosis is a specific disease process which is both infectious and contagious. The most characteristic feature of this disease entity is a benign hyperleucocytosis due to a relative and absolute increase of the small lymphocytes. The morphology of these lymphocytes is normal in all respects and the leucocytosis persists for approximately two to seven weeks.⁷⁻⁹ The clinical symptoms are generally mild, but in certain instances they have been severe enough to warrant active medical care and hospitalization.² Of particular interest is the general paucity of physical findings, particularly the absence of lymphadenopathy and splenomegaly. The Paul-Bunnel test is regularly negative.

In 1941 Reyersbach and Lenert⁶ reported from a children's convalescent rheumatic home sixteen cases of asymptomatic hyperleucocytosis with a predominating lymphocytosis. Although the abnormal cell type typical for infectious mononucleosis was absent and the Paul-Bunnel test was negative in all cases, they regarded this outbreak as an aberrant form of infectious mononucleosis. To substantiate their contention, they cited a case reported by Wilson and Cunningham¹¹ as an instance of infectious mononucleosis without signs or symptoms. This latter case was identical to the series of Reyersbach and Lenert in all respects, but no heterophile test had been done. The first complete description of this disease entity was presented by Smith.⁷ In a two-case report the author laid down the principles for this disease and its differential diagnosis. At this time Smith established the disease as a separate entity and designated it as acute infectious lymphocytosis.

Duncan¹ was the first to report a case of acute infectious lymphocytosis associated with symptoms and physical signs. At the onset abdominal complaints and findings were evident and during the first week suggestive neurological involvement was observed. The abdominal complaints were fleeting in nature and were attributed to a hyperplasia of the mesenteric lymph nodes, while the neurologic changes and the accompanying fever were regarded as part of a generalized illness.

In 1944 Smith⁸ reported four additional cases of acute infectious lymphocytosis. The communicability and the infectious nature of this disease was demonstrated. At this time the author discussed in greater detail the various aspects of the illness and presented further confirmatory evidence that the disease constituted a specific entity and could readily be separated from associated syndromes and blood disorders.

Since the classic papers by Smith,^{7, 8} a number of additional cases have appeared in literature.^{2-4, 12} The majority of the cases have been observed in children, although in three instances young adults have shown evidence of acute infectious lymphocytosis.^{2, 4} A most complete survey of this disease is included in a recent monograph.⁹

*From the Pediatric service of Sea View Hospital.

*Formerly Resident in Pediatrics, Sea View Hospital, Staten Island, N. Y.

CASE REPORT

K. B., a 5-year-old Negro female, was admitted to a hospital on July 18, 1946, with the chief complaint of pain in the abdomen and knees of three days' duration. The physical examination revealed a slight cardiac enlargement, a blowing apical systolic murmur, and a temperature 102.4° F. The x-ray on admission was interpreted as showing a pneumonic infiltration in the right upper lung field. The infiltration persisted and when a positive Mantoux was discovered the diagnosis of pulmonary tuberculosis was established. The patient was transferred to the Pediatric Division of Sea View Hospital on Oct. 3, 1946.

The past history was entirely negative. Birth and developmental course were not remarkable. The mother states that the child had been entirely well until July, 1946, at which time the fever was first noted. No additional history could be obtained.

The only notable finding on admission to Sea View Hospital was a small umbilical hernia. The other findings were within normal limits. The admission laboratory studies revealed a normal urine; feces and gastric specimens were negative for acid-fast bacilli; sedimentation rate was 11 mm. per hour; blood sugar was 95 mg. per cent and urea nitrogen 11 mg. per cent; Wassermann test was negative; red blood cells were 3.82, hemoglobin 10 Gm. or 69 per cent; white blood cells 9,700, polymorphonuclears 41, lymphocytes 56, monocytes 1, nonsegmented polymorphonuclears 2, eosinophiles 0; Schick test was positive; and Mantoux was positive (1:1,000,000). The admission x-ray of the chest was interpreted as revealing a small nodular focus of infiltration in the mesial portion of the upper lobe of the right lung. No evidence of cavitation or consolidation was seen, nor was there any enlargement of the mediastinum or paratracheal nodes.

Course.—The patient's hospital course was very mild save for a few intercurrent infections and one episode of phlyctenular conjunctivitis. In July, 1947, a dermatitis of the scalp was noted. These lesions revealed a greenish fluorescence under the Wood's light and the diagnosis of tinea capitis was made. The lesions persisted despite vigorous therapy, and in January, 1948, they were observed to be secondarily infected with resultant postauricular adenopathy. The child was placed on a regime of scalp scrubs with tincture of green soap twice daily. The skin lesions responded well and were soon healed with a concomitant reduction in the size of the lymph nodes draining this area.

Throughout her course the patient had been afebrile and had shown a progressive weight gain. Monthly gastric aspirations were all negative for acid-fast bacilli, and the chest, viewed roentgenologically, revealed a resolution of the pulmonary lesion. In view of these findings the child was re-evaluated for discharge in February, 1948. A blood count taken on Feb. 9, 1948, showed a red blood cell count of 4.57; hemoglobin 12 Gm. or 83 per cent; white blood cells 64,750, with segmented polymorphonuclears 9, eosinophiles 5, lymphocytes 87, basophiles 0, nonsegmented polymorphonuclears 0, monocytes 0. A repeat blood count on the following day revealed 60,400 white blood cells, polymorphonuclears 14, lymphocytes 85, monocytes 1, nonsegmented polymorphonuclears 0, eosinophiles 0, and basophiles 0. A sternal marrow smear taken at this time revealed a predominance of the small mature lymphocytic forms. (See Table II.)

Daily physical examinations were carried out in order to determine the etiology of the elevated white blood cell count. These examinations were all negative. The child's temperature remained normal. A review of the patient's course revealed no illness or temperature elevations during the two

TABLE I. K. B.: BLOOD COUNTS PRIOR TO, DURING, AND AFTER ACUTE INFECTIOUS LYMPHOCYTOSIS

DATE	R.B.C.	HGB. (%)	HGB. (GM.)	W.B.C.	POLY- MORPHO- CLEAR	LYMPHO- CYTES	MONO- CYTES	NONSEG- MENTED POLY- MORPHO- NUCLEARS	EOSINO- PHILES	BASO- PHILES
10/17/46	3.82	69	10	9,700	41	56	1	2	0	0
1/17/47	3.29	69	10	11,050	55	40	3	1	2	0
10/21/47	3.23	62	9	10,900	73	19	6	2	0	0
2/ 9/48	4.57	83	12	64,750	9	89	0	0	5	0
2/10/48	—	—	—	60,400	14	85	1	0	0	0
2/16/48	—	—	—	59,700	21	73	0	2	4	0
2/25/48	4.01	86	12.5	10,400	23	68	1	1	7	0
2/27/48	—	—	—	10,350	31	62	3	1	3	0
3/ 2/48	3.56	72	10.5	9,750	51	38	7	2	3	0
3/ 5/48	—	—	—	11,750	51	41	0	1	7	0
3/12/48	—	—	—	11,400	46	44	1	2	7	0
3/19/48	—	—	—	9,400	32	58	0	2	8	0
4/ 7/48	3.56	69	10	10,600	57	35	0	1	7	0
6/18/48	—	—	—	8,700	50	44	2	1	3	0
6/30/48	3.80	76	11	6,800	37	55	1	0	6	1

Discharged July 1948.

months preceding the leucocytosis. Serial roentgenograms failed to demonstrate an exacerbation of the healing tuberculous lesion. The child was closely observed for isolated episodes or paroxysms of coughing, but the clinical picture was entirely negative for pertussis. Nose and throat cultures, as well as a cough plate on special media failed to reveal any *Hemophilus* organisms. Further studies on the patient disclosed an erythrocyte sedimentation rate of 13 mm. per hour; bleeding time two minutes; clotting time 2.5 minutes, and repeated urines were essentially negative. Blood drawn for a heterophile serologic study was reported as negative. After Feb. 10, 1948, there was a gradual reduction of the total leucocyte and lymphocyte count until normal levels were reached on Feb. 25, 1948. A sternal marrow smear taken on March 5, 1948, was interpreted as being entirely normal. (See Table II.) All blood smears were closely studied, but in no instance were the large abnormal mononuclear cells characteristic of infectious mononucleosis seen.

TABLE II. K. B.: STERNAL MARROW CELL COUNTS*

CELL TYPES	FEB. 13, 1948	MARCH 5, 1948
Polymorphonuclears, nonsegmented	11.5	20
Polymorphonuclears, segmented	1.5	24
Neutrophilic myelocytes	15.5	15
Eosinophilic myelocytes	7	5
Metamyelocytes	2	2
Normoblasts	12	5
Small lymphocytes	50.5	29
Total	100.0	100.0

*These figures represent the frequency of occurrence per 100 cells counted.

In the four-month period following the discovery of this abnormal blood count the child remained entirely well and was subsequently discharged from the hospital. The diagnoses considered during the illness included infectious mononucleosis, acute infectious lymphocytosis, acute and chronic lymphatic leucemia, pertussis, an exacerbation of the tuberculous process, and an aberrant stimulation of the bone marrow as a result of the intermittent exposure to the Wood's light rays.

DIFFERENTIAL DIAGNOSIS

At the time the elevated white blood count was discovered, the main problem was one of differential diagnosis. A complete review of the child's course for the preceding two-month period and the entirely negative physical examinations helped to rule out the intercurrent and contagious diseases of childhood. Because of negative tests for heterophile antibodies and in the absence of typical blood findings, lymphadenopathy, and splenomegaly, infectious mononucleosis was eliminated as a possible diagnosis. Pertussis was unlikely because of the negative cough plate and negative nose and throat cultures for the *Hemophilus* organisms, as well as the total absence of the characteristic paroxysmal cough. Acute lymphoblastic leucemia was regarded as unlikely because the characteristically large, immature forms were absent in the peripheral blood and bone marrow smears. The uniformity and size of the lymphocytic cells, as well as the subsequently normal blood counts was unequivocal evidence against this fatal blood disease. Chronic lymphatic leucemia more closely resembles acute infectious lymphocytosis in cell morphology. However, this blood disorder was unlikely because of the absence of the usual clinical findings (lymphadenopathy, splenomegaly, anemia, and thrombocytopenia), and the return of a normal blood picture.^{8, 9}

It is a well-known fact that lymphocytosis is commonly seen in cases of tuberculosis and a combination of leucocytosis with lymphocytosis accompanies the spread of this infection. However, in this patient the clinical picture was normal throughout, and the laboratory studies and x-rays of the various organ systems showed no exacerbation or further tuberculous involvement.

Another factor in the differential diagnosis was the physical or chemical stimulation of the bone marrow by repeated exposure to the Wood's lamp. A careful review of the literature failed to reveal any previous reports of this type of blood picture response. However, it is well known that the marrow system may respond to diverse physical and chemical stimuli. Prior to the hyperleucocytosis, discovered in Feb., 1948, the child had been observed under the Wood's light two or three times a week. Each exposure lasted approximately 30 to 45 seconds, and in no instance was it prolonged over one minute. Because of the possible etiological effect of this physical ray, the child was no longer observed under the Wood's lamp. By Feb. 25, 1948, the blood picture was normal again. In order to test the hypothesis, the child was exposed daily to the Wood's rays for a two-minute period. This procedure was performed for a ten-day period. During this interval the peripheral blood remained within normal limits. On the eleventh day of exposure a sternal marrow smear was interpreted as being entirely normal. (See Table II.) Thereafter, the child was exposed to these rays three times weekly for two-minute periods. No further abnormalities were observed.

Another physical stimulus to which the patient had been exposed was the radiation of the x-ray machine. This influence can readily be discarded because of the relatively long intervals (three months) between exposures and the failure to observe further hemic abnormalities during subsequent radiation.

The final diagnosis was acute infectious lymphocytosis. Not only were the diseases considered in the differential diagnosis refuted by the clinical and laboratory data, but the observations made in this case coincided with the criteria set up for acute infectious lymphocytosis.

COMMENT

In the few years that have elapsed since Smith's recognition of this syndrome,¹ about fifty cases have appeared in the literature.⁹ Of these, twenty-

one cases observed by Finucane and Phillips³ were on the wards of a tuberculosis sanitorium. Martens⁵ has recently reported an additional twenty-two cases of acute infectious lymphocytosis from a Swiss hospital for tuberculous children. Whether or not tuberculous patients have a predisposition to developing acute infectious lymphocytosis will become the subject of a subsequent report.

Another remarkable feature of this case was the height (maximum of 64,750 leucocytes per cubic centimeter) to which the blood count rose. Smith⁹ and others have stated that the highest incidence of this disease is in children from one to 14 years of age. Smith places the peak within the first ten years of life. To date, only three cases have been reported outside of this age range, all of whom were within the third decade of life.^{2, 12} Close scrutiny of the published cases reveals an inverse relationship between the age of the patient and the height of the leucocyte count. The highest counts were generally observed in the youngest patients. This phenomenon was observed in our patient and lends further strength to this concept.

In previous reports, Finucane and Phillips,³ Smith,⁹ and Isreals⁴ have noted an increase in the eosinophilic leucocytes during the course of the disease. Finucane and Phillips state that the eosinophilia occurs at the peak of the white blood count, or shortly thereafter. The duration of the eosinophilia has been variable. In the case reported by Isreals the number of eosinophiles returned to a more normal level with the resumption of normal leucocyte counts. Finucane and Phillips observed eosinophilia for a seven-month period. In the reported case an increase in the eosinophilic leucocytes was noted throughout the more acute phases, and persisted for over five months to the time of discharge.

SUMMARY

1. A brief review of the origin and establishment of this disease entity is presented.
2. A case closely followed is presented to augment approximately fifty cases appearing in the literature.
3. The etiological significance of various physical agents, e.g., the Wood's light, are considered in detail.
4. The possible relationship and frequent occurrence of acute infectious lymphocytosis in tuberculous individuals is noted.
5. Mention is made of a persisting eosinophilia following the return to more normal leucocytic counts.

REFERENCES

1. Duncan, P. A.: Acute Infectious Lymphocytosis, *Am. J. Dis. Child.* 66: 267-271, 1943.
2. Duncan, P. A.: Acute Infectious Lymphocytosis in Young Adults, *New England J. Med.* 233: 177-179, 1945.
3. Finucane, D. L., and Phillips, R. S.: Infectious Lymphocytosis, *Am. J. Dis. Child.* 68: 301-308, 1944.
4. Isreals, S.: Acute Infectious Lymphocytosis, *Am. J. Dis. Child.* 74: 722-725, 1947.
5. Martens, von E.: Akute infektiöse Lymphozytose (Anstaltsepidemic bei 22 Kindern), *Helvetica Paediatrica Acta* 3: 220-224, 1948.
6. Reyersbach, G., and Lenert, T. F.: Infectious Mononucleosis Without Clinical Signs or Symptoms, *Am. J. Dis. Child.* 61: 237-244, 1941.
7. Smith, C. H.: Infectious Lymphocytosis, *Am. J. Dis. Child.* 62: 231-262, 1941.
8. Smith, C. H.: Acute Infectious Lymphocytosis: A Specific Infection, *J. A. M. A.* 125: 342-349, 1944.
9. Smith, C. H.: Acute Infectious Lymphocytosis Advances in Pediatrics, Vol. II, New York, N. Y., 1947, Interscience Publishers, Inc., pp. 64-92.
10. Thelander, H. E., and Shaw, E. B.: Infectious Mononucleosis With Special References to Cerebral Complications, *Am. J. Dis. Child.* 61: 1131-1145, 1941.
11. Wilson, C. P., and Cunningham, R. S.: A Consideration of Supravital Method of Studying Blood in Cases of Mononucleosis, *Folia Haemat.* 38: 14-29, 1929.
12. Yuskis, A. S.: Acute Infectious Lymphocytosis in an Adult, *J. A. M. A.* 132: 638-640, 1946.

SERIOUS TOXIC REACTION ASSOCIATED WITH ADMINISTRATION OF BAL

JEFFERSON D. BEALE, JR., M.D., AND DAVID I. SCHRUM, M.D.
WINSTON-SALEM, N. C.

BAL has been widely used in the treatment of heavy metal poisoning. Recently Warkany and Hubbard,¹ Bivings and Lewis,² and Elmore³ have reported its use in aerodynia. None of these reports has mentioned a "shocklike" state as occurring during BAL administration.

The following case, illustrating the occurrence of repeated peripheral vascular collapse in a patient receiving BAL, seemed sufficiently important to warrant reporting.

CASE REPORT

F. H., a 15-month-old white female infant, was admitted to the Pediatric Service of the North Carolina Baptist Hospital Oct. 4, 1948, with the complaint that during the previous month the child had "lost her appetite, had lost 6½ pounds of weight, had stopped walking and talking, and had developed a red rash on her feet and hands."

She had been perfectly well until one month prior to entry, when she developed anorexia, became irritable, and developed oliguria. She had no fever. The family physician found "pus" in her urine and gave her sulfadiazine for two days. After this she became weak, the anorexia increased, and she stopped walking and talking.

One week before admission her palms and soles became bright red, and an erythematous rash spread over her lower extremities, abdomen, and back. She rubbed her palms and soles constantly, assumed bizarre positions, perspired freely, and cried out when handled.

Past History.—She had four or five episodes of cyanosis during her second week of life, but otherwise had been well and developed normally. A history of contact with mercury could not be elicited. She had not had teething powders, calomel, treatment for "worms," nor local applications containing mercury.

Physical Examination.—On admission her temperature was 98.6° F. rectally; pulse was 120 per minute; respirations, 24 per minute; and blood pressure, 144 systolic and 104 diastolic. General examination revealed a miserable, poorly nourished female infant with bright red, peeling palms and soles, and an erythematous, macular rash on her lower extremities, abdomen, and sacral region. Respiration was increased, and marked hypotonia was present. Two lower incisor teeth were loose. She had no photophobia nor alopecia. There was no question about the diagnosis of aerodynia.

Laboratory Findings.—Urinalysis was negative; hemoglobin, 13.5 Gm. per 100 c.c.; red blood count, 4.53 million per cubic millimeter; white blood count, 11,500 per cubic millimeter with a differential of 46 per cent segmented polymorphonuclear neutrophiles; 2 per cent nonsegmented polymorphonuclear neutrophiles; 48 per cent lymphocytes; and 4 per cent monocytes. Blood Kahn was negative. Stool examination was negative for blood, ova, and parasites.

Progress.—The first week in the hospital the patient received supportive therapy, and her general condition was unchanged. Her blood pressure re-

From the Department of Pediatrics of the Bowman Gray School of Medicine of Wake Forest College and the Pediatric Service of the North Carolina Baptist Hospital, Winston-Salem 7, N. C.

mained elevated and she slept only one-half to two hours a day. She developed conjunctivitis.

On October 12, eight days after admission, she developed physical and x-ray findings of pneumonitis in both lower lung fields. She was given 300,000 units of Duracillin daily. Although her temperature returned to normal in three days, her general condition became worse. Four loose teeth fell out of her mouth. Anorexia became so severe that gavage feedings were necessary.

One hundred cubic centimeters of urine⁴ obtained in a mercury-free container on October 10 were found to contain 370 µg of mercury per liter. This was considered a "very large" amount.

On October 18, fourteen days after admission, she was started on intramuscular BAL 10 per cent with benzyl benzoate 20 per cent in peanut oil. The dosage schedule used by Elmore³ was started. This schedule consists of giving intramuscular BAL 2.5 mg. per kilogram and 0.5 c.c. of 2 per cent procaine every four hours for twelve hours, then every six hours for forty-eight hours, and then every twelve hours for eight additional days.

On October 19, after seven doses of BAL with procaine, she became very listless, vomited several times, had increased salivation, had six foul, watery, greenish-yellow stools, and her temperature became elevated. The next morning, two hours after the tenth dose of BAL, her temperature was 102.4° F. rectally and she appeared to be in shock with cold, clammy extremities, and had a feeble heart action with a rate of 200. The radial pulse was not palpable, and the blood pressure could not be obtained. Blood studies at that time revealed a carbon-dioxide combining power of 16.7 meq. per liter (37 volumes per cent) and chlorides of 91.5 meq. per liter (536 mg. per cent). Her hemoglobin was 11 Gm. per 100 c.c. and white blood count 26,800 per cubic millimeter. Plasma, 5 per cent glucose in distilled water, and whole blood were given intravenously, and the peripheral circulation improved. Her temperature rose to 106° F. rectally, but returned to normal within sixteen hours. Blood culture was negative. She was again put on prophylactic doses of penicillin.

During the next four days she seemed to improve generally. The erythema of the palms and soles decreased, and she took her feedings better.

On October 24 the patient was given one test dose of 17.5 mg. of BAL and 0.5 c.c. of procaine intramuscularly without reaction. This was repeated on October 25 without reaction. On October 26 the original dosage schedule as previously described was resumed.

On November 2, after seventeen injections of BAL, she became listless, vomited, and developed diarrhea. Blood studies at that time revealed a carbon-dioxide combining power of 15.8 meq. per liter (35 volumes per cent), hemoglobin of 15 Gm. per 100 c.c. of blood, and white blood count of 18,850 per cubic millimeter. BAL was stopped, and twelve hours later she presented a picture of shock identical with the first episode except that her temperature rose only to 104.2° F. rectally. She again recovered after the intravenous administration of plasma, normal saline, and 5 per cent glucose in distilled water. On November 3, sixteen days after institution of BAL therapy, her urine contained 100 µg of mercury per liter.

She developed two episodes of pulmonary congestion manifested by numerous moist râles scattered throughout the lung fields, following vigorous and rapid administration of intravenous fluids. The remainder of her hospital course was uneventful. She was discharged on November 23, improved.

On December 7 she was seen in the Outpatient Department and improvement had continued.

⁴The mercury determinations on the urines were done by Dr. Josef Warkany and Mr. Donald Hubbard of the Children's Hospital Research Foundation, Cincinnati, Ohio.

COMMENT

This case demonstrated the occurrence of a "shocklike" state in a patient receiving BAL. A definite association between BAL administration and the clinical picture of shock in this patient was not established. Procaine or the preservative benzyl benzoate may have contributed to this infant's reaction. Although the mechanism of collapse in this patient was not definitely determined, certain possibilities were considered. The effect of BAL on the autonomic nervous system with a vasomotor response resulting in peripheral collapse could explain the shocklike picture in the patient. The relationship between the blood volume and urine output and fluid intake has also been considered as an explanation for the peripheral collapse. The function of the adrenal cortex could also be affected by BAL and result in this type of peripheral vascular collapse.

SUMMARY

A case is reported of an infant who developed peripheral vascular collapse on two occasions while receiving BAL. Although BAL may prove to be a beneficial agent in the treatment of acrodynia, this case report suggested the possibility that BAL may cause serious toxic reactions in some patients.

REFERENCES

1. Warkany, Josef, and Hubbard, Donald M.: Mercury in the Urine of Children with Acrodynia, *Lancet*, 1: 829, 1948.
2. Bivings, Lee, and Lewis, George: Acrodynia: A New Treatment with BAL, *J. PEDIAT.* 32: 63, 1948.
3. Elmore, Samuel E.: Ingestion of Mercury as a Probable Cause of Acrodynia and Its Treatment with Dimercaprol (BAL): Report of Two Cases, *Pediatrics*, 1: 643, 1948.

Clinical Conference

CONFERENCE AT THE UNIVERSITY OF ARKANSAS HOSPITAL*

WILLIAM A. REILLY, PROFESSOR AND HEAD OF PEDIATRICS

Case 1. Typhus Fever

DR. A. KRIEGER (Intern).—J. L. (private patient of Dr. Sam Phillips, Baptist Hospital), a male infant, aged 16 months, was taken ill Dec. 17, 1948, with listlessness and slight fever; two days later a petechial rash came out on the feet, legs, forearms, hands, and face, and gradually spread over the rest of the body; on the eighth day swelling began on the ankles and spread over the body. His fever rose soon after onset to 102 to 104° F., which it was at admission on Dec. 26, 1948. He had been playing with wild animals, made pets. There were numerous rats in his home.

The family and past history did not reveal any significant facts.

On admission on the ninth disease day he appeared well developed and nourished, lying quietly but somewhat stuporous. There was generalized mild edema. Petechial hemorrhages were seen in the skin over all the body and in the mucosa of the mouth; the throat was injected. There were no meningeal signs, adenopathy, or hepatosplenomegaly. The remainder of the physical examination was not remarkable.

The clinical impression was that he had typhus fever.

Laboratory Findings.—Repeated urinalysis showed occasional traces of albumin and rare casts. There was moderate hypochromic anemia with hemoglobin of 75 to 55 per cent and 3.95 to 3.2 million red blood cells. The white blood cells ranged between 17,500 to 22,000 with 70 to 84 per cent neutrophils during the first hospital week to 13,000 to 15,000 with 55 to 65 per cent neutrophils during the last week in the hospital when fever was slowly disappearing (twenty-sixth to thirty-third day of disease). The Weil-Felix blood agglutination with *Proteus OX19* was positive on the tenth disease day at the 1-400 dilution and on the thirteenth day the positive dilution had increased to the 1-800 dilution. A blood culture on admission was still negative after fourteen days. Agglutinin tests for typhoid, paratyphoid, and undulant fever organisms were negative on admission.

Course and Treatment.—The boy remained acutely ill and stuporous, had muscular twitching, some right-sided spasticity, strabismus, and irregular, rapid respiration. A new rash came out and he had to be tube fed during the first hospital week (ninth to sixteenth disease days). The rash disappeared by the twentieth day. In general, he improved markedly after that time but there was some residual spasticity and nervousness. Fever came down gradually over a course of twenty-eight days from onset of first symptoms. There was a mild diarrhea from the seventeenth to nineteenth disease days.

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Penicillin was given during the first two hospital days. Sulfadiazine (2.0 Gm. daily) was given from the twelfth to eighteenth hospital days. Aureomycin (Duomycine of Lederle Laboratories) was started on the eleventh disease day by stomach tube, 750 mg. for the first dose and 250 mg. every four hours for two doses; then 60 mg. of it were given intramuscularly every four hours for the next seven days (until the eighteenth day). There was sudden and marked improvement soon after starting aureomycin, for he changed from a critical state to one with less stupor and twitchings; drowsiness started then. Two supportive transfusions were given on the twelfth and fourteenth disease days.

When last seen, eight weeks after onset, all spasticity, inability to focus his eyes, nervousness, etc., had disappeared.

DR. PHILLIPS (Associate Professor of Pediatrics).—Typhus or meningococcus were considered the most likely causes. The latter did not seem to be the cause, because when I first saw him on the ninth disease day as yet there were no meningeal signs, the rash was more petechial than purpuric. It is true that later he developed strabismus and right-sided spasticity. Yet in the meantime he had been on doses of sulfadiazine adequate to control such a meningitis and had some penicillin. A blood culture, too, was negative. The points in favor of typhus fever were: the onset with fever and listlessness and the appearance of the rash on the second day. The rash at onset may have been pinkish-red, as in typhus macules; on entry it was petechial and widespread, as in typhus fever. It started on the limbs as in Rocky Mountain fever.

The profound stupor, critical condition, the injected conjunctivae and coated tongue are characteristic of typhus. When the Weil-Felix reaction was so strong and became more so three days later, we were certain of typhus as the cause. The presence of rats and wild animal pets were other helpful points; no other cases have occurred in the area. No louse or flea bites were found on the child.

Dr. William A. Reilly suggested the use of aureomycin. The boy was profoundly ill and improved rapidly and greatly when aureomycin was given. His fever, which had been on a plateau for some days, gradually came down during the time aureomycin was given (seven days). Sulfadiazine was used during the same time; it may be that another infectious agent was complicating the picture and that continued usage of sulfadiazine might have stopped fever sooner, for it continued for seven days after both drugs were stopped. It is thought that typhus fever is stopped in several days by aureomycin and that only five to seven days' therapy with it is all that is needed.

DR. REILLY.—This boy had a clinical picture of typhus very similar to the great numbers I had seen in French Morocco. The fever was a bit long, twenty-eight days, for endemic typhus which we have in Arkansas, but I think that he likely may have had a complication with another organism. It was not possible to do a guinea pig inoculation or blood tests for rickettsial agglutinations, neutralizing antibodies, or complement fixation for differentiation of rickettsiae.

Typhus in Arkansas is diminishing yearly; the median number of cases between 1943-47 was nineteen yearly.

It is the endemic type, *Rickettsia mooseri*, which is rat-borne by the flea to the human; there is a mortality of about 2 per cent over the country; it is more common in winter, whereas Rocky Mountain fever occurs in the early spring and summer and has not been seen very often in Arkansas.

There are three "species" for rickettsial diseases—para-aminobenzoic acid, chloromycetin, and aureomycin. The first should be given in the first week of disease and is inferior to the other two. Chloromycetin¹ is very effective for the several typhus fevers and Rocky Mountain spotted fevers; it was not available. Aureomycin has been used successfully against Rocky Mountain fever. Smadel and associates² have shown this experimentally and clinically. Because of the similarities of the rickettsia of that disease and that of endemic typhus and the availability of aureomycin, we used it. The supply and monies for a purchase limited our use to seven days. The dose was 75 mg. per kilo on the first day. We reduced it thereafter to about 20 mg. per kilo daily. Some typhoid patients have received 300 to 500 mg. per kilo daily without untoward results; 50 to 100 mg. per kilo daily is an average dose. In therapeutic doses aureomycin is not toxic; occasionally nausea occurs. This patient had no ill effects. It is usually given orally; we gave it intramuscularly because the child could not cooperate due to stupor.

The boy seemed to be dying. A natural cure may start between the fourteenth and eighteenth day. Though the drug was given between the eleventh and eighteenth days, I am sure it was the cause of his improvement.

DR. PHILLIPS.—Recently I took care of another case of typhus fever. This girl was severely ill for five days with typical toxicity and rash. On the sixth day the *Proteus OX19* was positive in a dilution of 1:640. Chloromycetin was then started (50 mg. per pound per twenty-four hours). The temperature rapidly came down within forty-eight hours, the child's general condition improved, her stupor rapidly disappeared, and the rash vanished quickly. On the tenth day Weil-Felix reaction was positive to 1:1,280. The drug was stopped and no complications developed.

The two cases seemed to be of equal severity but the second case treated with chloromycetin seemed to recover more quickly than the first.

ADDENDUM

DR. REILLY.—Recently a third patient with typhus fever, type Rocky Mountain spotted fever, S.E. No. 85912, came to us on the fifth day of her disease. She had a typical history and rash and was quite ill. A number of ticks had bitten her. Chloromycetin was started in the same dosage as above on the seventh day; by the tenth day the fever had left. Recovery was uneventful.

Case 2. Esophageal Atresia With Tracheoesophageal Fistula; Successful Operation

DR. JOHN A. HARREL, JR. (Assistant Resident in Pediatrics).—This female infant was born at 8 A.M. Feb. 20, 1949. The child was apparently in good condition at birth and had no trouble until twelve hours after birth when the

first feeding was attempted. She took only a small amount when she strangulated and regurgitated. She had cyanotic spells following this and very thick mucus in the throat which would flow freely from the mouth. The child was then brought to our emergency room. Examination revealed a normal full-term infant who was having no respiratory difficulty but who had considerable whitish, thick mucus in throat and mouth. This was aspirated. The child was given a trial feeding of distilled water and after taking only a few swallows, regurgitated and became choked. She was then taken to x-ray and a small catheter was inserted into the esophagus; it could not be passed beyond the upper third. A small amount of Lipiodol was injected. Fluoroscopy and spot films (Fig. 1) revealed a smooth, abrupt closure of the thoracic esophagus at about the level of the carina. Filling of the bronchi did not occur. A lower esophageal segment was not visualized. An air bubble was in the stomach.



Fig. 1.—Case 2, showing a good excursion of the proximal esophageal segment.

The mother was 18 years old and the father was 21 years old. This was the first child. Total labor was nine hours. Serology was negative on both the mother and father. The mother had no illnesses during pregnancy, and had

approximately eight months' gestation. The infant's weight was 6 pounds, 9 ounces at birth.

Physical examination was quite negative. No dehydration had yet developed. Heart, lungs, and abdomen particularly were normal. There was no anemia.



Fig. 2.—Case 2. Postoperative appearance showing patent, nonleaking anastomosis.

Hydration was maintained by parental injection of lactated Ringer's solution. At the age of 36 hours, Dr. James Growden elected to do a right extrapleural approach to the esophagus. The roentgenogram showed that the dilated upper esophageal segment was capable of moving to practically the lower third of the thorax and, therefore, it was likely that an anastomosis was possible, presuming that a reasonable amount of lower segment was present.

Local anesthesia was started. A tracheal fistula just above the carina was found; the lower esophageal segment was found large enough to permit anastomosis and the dilated upper esophageal segment was found connected by serosa to the lower segment. Ether anesthesia with positive pressure was then started. The fistula was closed and the lower segment freed and anastomosed to the upper. A polyethylene catheter was placed in an ankle vein before operation and fluid and blood were given.

Postoperatively the infant did very well. A small amount of serosanguineous fluid and air had to be removed from the right thorax one day after surgery. Feedings consisted of parenteral fluids and blood through the indwelling catheter. On the fourth day a small amount of Lipiodol by mouth showed (Fig. 2) a patent, nonleaking, normally functioning anastomosis. A gastrostomy was done on that day for a feeding route and possible retrograde dilatations. Feeding was started on the fifth day. Purposefully no oral feedings were hazarded until the twelfth postoperative day. No difficulties were encountered with these oral feedings and the baby has progressed satisfactorily in all respects.

DR. REILLY.—Dr. Harrel is to be commended for his prompt recognition of an esophageal atresia and tracheoesophageal fistula.

We encountered a similar case two months before which was widely discussed. The general condition of the patient prevented exploration of chest. The most that could be done was a gastrostomy and exteriorization of upper blind esophagus, for the segments could not even have been approximated, as the autopsy confirmed.

The most common defect (in 70 to 80 per cent of cases) consists of a blind upper segment and a connection of the lower segment to the trachea just above its bifurcation. This defect has a characteristic sequence which should stay in memory, rare though it is (one in about 10,000 births): profuse mucus drooling from the mouth, vomiting the first and all subsequent feedings as soon as the few small swallows go into the esophagus, usually choking, coughing, and cyanosis with the vomiting, and the presence of bile and particularly gastric secretion. The baby may be quite all right otherwise for several days or until pneumonia and starvation set in. The excessive mucus comes from the lung due to the irritation of foreign matter such as food, bile, and gastric juice. Mucus before feeds have been taken may, therefore, indicate fistulous connection to the esophagus just as does bile in vomitus and air in the stomach. These three findings are diagnostic aids. The point where a catheter stops will help in diagnosis as well as locate the lower level of the upper segment. One should use Lipiodol rather than barium for visualization, for the latter is more irritating if it is thrown into the lung by regurgitation; it would be well to use only a bit of Lipiodol and try to aspirate that after the roentgen examination.

There are several other varieties of complete atresias which we will not consider.

The esophageal atresias can now be approached operatively and this major undertaking should be considered separately for each case. Early recognition is paramount; otherwise drowning or pneumonia could defeat any successful operative approximation of the esophageal segments. Such an approximation depends on the amount of mobility of the segments, nature of wall, and size of lower segment, which is usually sufficient in most cases, and the amount and type of tissue in the lower segment to work with. Occasionally this consists of only a thin cord impossible to anastomose. Prior roentgen visualization will give a good estimate; examination at exploration may be the only way to tell. This is justified, for the baby will surely die if denied the benefit of exploration. Most of the experienced surgeons like Haight and Towsley,³ feel that once the diagnosis is made operation should be done as soon as dehydration or anemia is corrected. Aspiration of the extra mucus and medication for a pneumonia or other fever, if present, should be undertaken. This should require only about one day. Haight recommends a one-stage operation through an extrapleural approach, closing the fistula and anastomosing the ends of the segments.

DR. JAMES H. GROWDON (Assistant Professor of Surgery).—The enthusiasm for surgical treatment of congenital atresia of the esophagus with tracheoesophageal fistula was not so great until recent years, when Haight, Ladd and Gross, and others showed that primary anastomosis of esophagus within the thoracic cage was feasible in perhaps 60 to 75 per cent of cases. This results in a relatively normal situation. Methods which entailed the construction of an extra thoracic esophagus were long, tedious, and often not too satisfactory.

Once diagnosis is made, thoracotomy is indicated as early as possible to determine the feasibility of such a procedure. As Dr. Reilly has indicated, this will depend usually on the length and mobility of the upper segment and the length and size of the upper portion of the lower segment of the esophagus. The walls of the lower segment may be very thin and poorly developed. Where a primary anastomosis is not feasible, the upper segment should be brought out the lower neck in anticipation of later constructing an extrathoracic esophagus, and the fistulous connection between esophagus and trachea should be closed. A gastrostomy for feeding purposes may be performed within the next day or two.

In this case a gastrostomy has been performed for feeding purposes and will be maintained until it is ascertained when dilation of the anastomosis will be necessary in this patient. If this becomes necessary a gastrostomy will aid in passage of a thread to guide the bougies as in other esophageal strictures.

Case 3. Incomplete Rotation of Intestines With Duodenal Obstruction

DR. WILLIAM P. BARRON (Assistant Resident in Pediatrics).—L. W. is a 4-month-old white female infant. She weighed 7 pounds at birth. Delivery was spontaneous and uncomplicated in the home, attended by a midwife. The infant was put on the breast and did well for the first three weeks of life, weighing 9 pounds at the end of that time. At that time she began having postcibal

vomiting which occurred fifteen or thirty minutes after a feeding. At first the vomiting occurred one or two times a day but gradually increased until it occurred after almost every feeding. The vomitus was always characteristically bile-stained.

She was taken off the breast and put on several formulas, but the vomiting persisted and the patient began to lose weight rapidly.

She was first brought into this hospital at 3 months of age.



Fig 3.—Case 3. Note the dilated duodenum constricted (arrow) in its second and third portions.

Family History.—One child was born prematurely and died four days after birth. A 3-year-old child is apparently normal. A 2-year-old boy has been treated in the orthopedic clinic for congenital deformities of the lower extremities. The child is quite dark in color, with black, kinky hair and all the physical characteristics of a Negro, in marked contrast to his two blue-eyed, blonde sisters and parents.

On admission to the hospital, the physical examination revealed a markedly emaciated and dehydrated 3-month-old white female infant weighing 8 pounds, 6 ounces. She was quite irritable and appeared chronically ill. There was a

small umbilical hernia, the ring measuring one centimeter in diameter; there was also noted a soft mass 2.5 cm. in diameter in the right upper quadrant which moved slowly to the right with peristalsis. There were no other findings except a marked anemia.

Preoperatively she continued to vomit bile-stained vomitus fifteen to thirty minutes after eating. Her stools were fairly normal, pasty yellow or green. A gastrointestinal series (Fig. 3) revealed the swallowing function and the stomach to be normal but the duodenum was markedly dilated throughout the first portion. A constriction or partial obstruction was seen in the second and third portions of the duodenum. A barium enema showed the sigmoid to fill and extend toward the right side of the abdomen instead of to the left. There was a marked derangement of the normal pattern of the colon, and the terminal ilium was visualized in the right midabdomen.

An exploratory laparotomy was performed on the sixth hospital day after the patient's condition had been improved with whole blood transfusions and fluid administration.

Her postoperative course was uneventful and the patient began to take her formula without vomiting. She rapidly improved and gained weight and was discharged on the thirteenth postoperative day.

The mother brought the patient back to the hospital four days ago (one month postoperatively) with a history of vomiting and obstipation for the previous two days. She was slightly distended and it was thought that there may have been a complete or more probably a partial obstruction due to the other congenital adhesions. After thirty-six hours of observation she started passing gas per rectum, having bowel movements and retaining her feedings, so that it seems that the obstruction has been spontaneously relieved. A gastrointestinal series and barium enema made today showed no obstruction but there is still a narrowing at the duodenjejunal junction. The stomach was entirely empty at the end of three hours.

DR. REILLY.—There were several important findings here: In the neonatal period vomiting of gastric contents and bile persisted for nine weeks, leading to malnutrition and the finding of a mobile mass in the right upper quadrant, which was soft and changing in size. One should think of a bowel obstruction first and other intra-abdominal lesions thereafter. The umbilical hernia, of course, was suspected but did not seem to contain bowel during the episodes. Partial obstruction was indicated by the frequent vomiting, the moderate distension, and extra peristalsis, and the fact that feces were passed. The most important localizing finding was the bilious vomitus. Pyloric stenosis as a rule does not appear so soon (3 weeks) but could, of course; if any bile is present then it is minimal. This baby vomited much bile and usually this indicates obstruction below the ampulla of Vater. Distension is usually present and this was confirmed by the roentgenogram. The most common cause is congenital bands and this is associated with failure of rotation from the left fetal position to the right-sided position of the normal full-term baby. Usually the bands are in various parts of the small intestines. Complete exploration to

cut bands and correction of the malrotation is not always as possible as some of the tests seem to indicate. The barium enema gave us much information. The barium meal localized the higher defect in the second or third portion, the part of the duodenum more commonly involved. Usually bands are found in other parts of the bowel, as we suspected. Nevertheless, exploration for any relief is to be done after attempts to correct dehydration, shock and anemia etc., are carried out.

One might diagnose a high obstruction, without x-ray visualization, by the persistent vomiting of much bile and thus not hazard further obstruction due to retention of barium. We chanced barium in order to detect a more nearly true idea of abnormal conditions in the entire bowel.

DR. G. O. DEAN (Professor of Surgery).—With the peritoneal cavity adequately exposed through a long upper right rectus incision, it became evident that malrotation of the intestines was present. Upon superficial examination the condition appeared to be identical to one type of congenital malrotation described by Ladd and Gross.⁴ In their cases there were malrotation of the intestines, volvulus of the gut on the mesentery, and a constricting congenital peritoneal band extending from the right upper abdomen across the duodenum to the region of the cecum and appendix, which lay high and more or less in the midline of the peritoneal cavity just beneath the stomach.

Following the precepts of Ladd and Gross, all intestines were delivered through the incision. Then an exhaustive attempt was made to unwind the apparent volvulus, to dissect away the constricting peritoneal band, and to thereby relieve the duodenal obstruction and all obstructing mechanisms caused by volvulus, malrotation, or peritoneal bands.

However, after a period of careful dissection and cutting of all constricting peritoneal bands and thorough attention to all possibilities of unwinding the apparent volvulus, it was revealed that an additional abnormality was present in this patient. The third portion of the duodenum was being constricted by two ligamentous-like peritoneal folds which extended into and were continuous with the mesentery of the small and large bowel. The duodenum appeared to be piercing the mesentery of the bowel. The presence of a large artery and vein in each of the ligamentous peritoneal folds further complicated the relief of the duodenal constriction. In other words, there were a large artery and vein in the fold which lay in front of the duodenum and also another large artery and vein lying in the fold behind the duodenum. These two large vessels were also observed to branch profusely in the mesentery and to serve as the combined blood supply for all the small bowel and most of the large bowel. Any effort to cut one or the other of the constricting peritoneal folds would have destroyed the blood supply to approximately one-half of the intestinal tract.

It was then found that additional dissection and tugging about the vessels at the root of the mesentery would give considerable relaxation in the constricting effect on the duodenum. Shortly thereafter, gas was observed to be passing freely from the distended duodenum into the upper jejunum.

Although it was evident that the constricting effect on the duodenum might easily recur as soon as postoperative adhesions formed or in the event that even slight torsion of the mesentery should ensue, a decision was made to consider the above operative procedures as adequate to relieve the obstruction. A gastrointestinal series eight days postoperatively showed some residual duodenal dilatation and slight barium retention in the stomach at the end of six hours. Another gastrointestinal series five months later revealed a persistent narrowing of the lumen in the distal portion of the duodenum, but no retention of barium after six hours. Eight months later the patient was seen with an upper respiratory tract infection and an associated diarrhea, but she had no signs or symptoms of intestinal obstruction.

Obviously, this patient may yet develop a recurrence of the constrictive mechanism at the distal end of the duodenum. If she does develop a recurrent duodenal obstruction, the treatment of choice will be side-to-side anastomosis between the third portion of the duodenum and a proximal loop of jejunum.

Perhaps the above anastomosis should have been done during the original operative procedure. At that time it was the surgeon's impression that such an anastomosis might be indicated, but the additional time that would be required and the necessity for opening an obstructed loop of bowel were factors that motivated the surgeon to be more conservative.

In regard to the "surgical indications," several conclusions can be drawn from this case. First, after such an anomaly begins to develop the later development of blood vessels, peritoneal bands, etc., will probably deviate still further from normal and the presence of such an anomaly precludes any certainty that it can be corrected by any routine or previously formalized surgical procedures. The surgeon is beset with the necessity of carefully and prodigiously dissecting and examining all involved structures before determining his complete operative procedure. Second, the long length of time consumed during the shocking exploratory procedures may prevent the safe consummation of some indicated corrective procedures. Third, contrary to the usual description of malrotation of the intestine, this case could not be completely relieved by derotation and the cutting of constricting bands. This was borne out in our experience with three similar cases, previously explored and operated. Fourth, this and similar cases may require short-circuiting anastomosis between the duodenum and proximal jejunum.

REFERENCES

1. Ross, G., Schoenback, E. B., Beirle, F. G., Bryer, M. S., Rice, E. C., and Washington, J. A.: Aureomycin Therapy of Rocky Mountain Spotted Fever, *J. A. M. A.* 138: 1213-1216, 1948.
2. Smadel, J. E., Leon, A. P., Levy, H. L., and Varela, C.: Chloromycetin in the Treatment of Patients With Typhus Fever, *Proc. Soc. Exper. Biol. & Med.* 68: 12, 1948. Smadel, J. E., Woodward, T. E., Ley, Jr., H. L., Philip, C. B., Trant, R., Lewthwaite, R., and Savoia, S. R.: Chloromycetin in the Treatment of Scrub Typhus, *Science* 108: 160, 1948.
3. Haight, C., and Towley, H. A.: Congenital Atresia of the Oesophagus With Tracheo-esophageal Fistula, *Surg., Gynec. & Obst.* 76: 672-688, 1943.
4. Ladd, W. E., and Gross, R. E.: *Abdominal Surgery of Infancy and Childhood*, Philadelphia, 1947, Chap. V., W. B. Saunders Company.

Psychologic Aspects of Pediatrics

EMOTIONAL DEPRIVATION IN INFANTS

HARRY BAKWIN, M.D.

NEW YORK, N. Y.

UNTIL the early years of this century, when it was the custom to keep homeless infants in institutions for custodial care, the babies quickly withered and died. Whether all perished or only most of them depended principally on one factor: the duration of their stay in the institution.

The high institutional mortality of infants was discussed at the annual meeting of the American Pediatric Society in 1915. Dr. Henry Chapin¹ reported on ten infant asylums located in different cities of the United States. In all but one institution every infant under 2 years of age died. Hamil² of Philadelphia, in discussing Chapin's paper, said ironically: "I had the honor to be connected with an institution in this city in which the mortality among all the infants under one year of age, when admitted to the institution and retained there for any length of time, was 100 per cent. That is, no infant admitted under one year of age lived to be two years old." Southworth,³ speaking for conditions in New York City, said: "I can give an instance from an institution that no longer exists in which, on account of the very considerable mortality among the infants admitted, it was customary to enter the condition of every infant on the admission card as hopeless. That covered all subsequent happenings." Knox⁴ described a study which he had made in Baltimore. He followed 200 infants admitted to various institutions in the city. Of these almost 90 per cent died within a year. The 10 per cent that lived, he said, did so, apparently, because, for some reason or other, the babies were taken from the institutions for short times and given into the care of foster parents or relatives.

SYMPTOMATOLOGY

Infants under 6 months of age who have been in an institution for some time present a well-defined picture. The outstanding features are listlessness, emaciation and pallor, relative immobility, quietness, unresponsiveness to stimuli like a smile or a coo, indifferent appetite, failure to gain weight properly despite the ingestion of diets which, in the home, are entirely adequate, frequent stools, poor sleep, an appearance of unhappiness, proneness to febrile episodes, absence of sucking habits.

The hospitalized infant is thin and pale but the pallor is not always associated with a reduction in the hemoglobin. The facial expression is unhappy and gives an impression of misery. Muscle tone is poor and it is possible to extend the legs fully at the knees, contrasting in this way with normal young infants. There is no alteration in the deep reflexes. The infant shows no in-

From the Department of Pediatrics, College of Medicine, New York University—Bellevue Medical Center.

terest in his environment, lying quietly in bed, rarely crying and moving very little. Such movements as he makes are slow and deliberate, unlike the quick movements one expects at this age. Even respiration seems quieter than in normal infants.

The appetite is indifferent and food is accepted without eagerness or interest. The weight may be stationary; there may be loss or slow gain. The amount of food necessary to effect a weight gain is much greater than in the home. Nevertheless growth in height continues at a rate only slightly less than average. The stools are frequent and, in sharp contrast to the situation in the home, it is unusual for twenty-four hours to pass without an evacuation.

Normal infants at 2 to 3 months of age smile and become animated in response to the smile or cooing voice of an attentive adult. Not so the baby who has been in a hospital for any length of time. Here it is difficult to elicit a smile in this way and repeated efforts are necessary. Sleep is light and fitful even at 3 and 4 months, resembling that of babies during the early weeks of life. Sucking habits are uncommon.

Temperature elevations, sometimes associated with mild respiratory infections, oftentimes without demonstrable cause, are frequent. We have observed babies who developed fever while in the hospital which persisted for months. We reported five infants in whom fever lasted for from three to eight months.⁵ The cause of the fever was investigated with every available laboratory test but nothing was found except an occasional red throat or running ear, infections which in the home last only a day or two. There was no response to chemotherapy. In all instances the temperature fell to normal when the infants were discharged from the hospital and it remained normal thereafter.

In severe cases the symptoms are intensified and the baby assumes the appearance of a wizened, toothless old man. The cheeks are sunken, although in some instances the sucking pads in the cheeks remain; the skin is loose and somewhat inelastic; the whitish pallor is striking and the general impression is one of great weakness and frailness. The respirations are slow and superficial and often sighing.

PREDISPOSING FACTORS

The duration of hospital stay preceding the appearance of symptoms varies considerably, some children showing definite changes within a few days after entry to the hospital, others remaining for weeks without becoming ill. Age is an important factor. We have never seen the clinical manifestations of emotional deprivation during the first two weeks of life which was the usual duration of the stay for mothers and babies in obstetrical hospitals before the war. Though most babies who are born in hospitals receive very little manipulation during this time they appear vigorous, they have lusty cries and good color, and they gain well. However, if a newborn baby remains in the hospital, for one reason or another, after the first month he generally shows symptoms of hospitalism.

As a rule, prematurely born infants, especially the small ones, are unaffected by the rigid isolation practiced in the modern premature unit. Only

when they remain in the hospital for a long time and have outgrown their prematurity do they show the physical and behavioral manifestations generally associated with emotional deprivation.

A possible predisposing factor is the nature of the illness for which the child enters the hospital. It has seemed to us that children with diarrhea are more susceptible than others, possibly because this is a rather prolonged illness and one which, in itself, interferes severely with the baby's nutrition.

Another factor may be the amount of emotional satisfaction which the child had received before entry to the hospital. A certain number of babies, reared in the home, show the pallor, the quietness, and the motor retardation which are associated with emotional deprivation. Such babies are likely to be left to themselves in the hospital while the attractive, animated ones receive the affectionate attention and interest of the hospital personnel.

Infants with gross cerebral damage are not affected by emotional deprivation. Of the several hundreds of such infants who have been admitted to Bellevue Hospital in the course of years we do not recall having seen a single one who showed the clinical picture described above. Instead, they sometimes develop hyperpyrexia and die within a few days after entering a hospital. This may take place in infants who at first appear to be in excellent nutritional condition. At home they have been cared for by attentive mothers who come to understand their peculiar behavior and who cater to them. In the hospital the nurses find the mannerisms of these children strange and unpredictable and unattractive. Feeding is especially difficult and consequently the food and especially the fluid intake is inadequate. In addition they may contract infections. Presumably the hyperpyrexia is a result of dehydration, infection, and a cerebral element ("cerebral fever").

The absence of symptoms in prematurely born infants, in newborn infants, and in infants with severe cerebral damage suggests that, though the clinical manifestations of this condition in early infancy are principally physical, a certain amount of conscious cerebral functioning is necessary in order for injury to register itself.

Certain physical considerations may contribute to the speed with which babies deteriorate in hospitals. They are unable to indicate satisfactorily when they are hungry and when they have had too much, and it is hardly possible for the nurses to understand the idiosyncracies of the individual infant on short acquaintance. Moreover, the prevalent custom of prescribing food in hospitals lacks the flexibility which is possible in the home. Rigid orders for feeding are given and there is no mechanism in most hospitals whereby the infant can have more of his formula at one feeding when he is hungry and not so much at another when he is satisfied with less. Food refused at one feeding cannot be made up at another.

The rapidity with which the symptoms of hospitalism begin to disappear when an afflicted baby is placed in a good home is amazing. It is convincing evidence of the etiologic relation of the emotionally arid atmosphere of the hospital to the symptoms. The baby promptly becomes more animated and

responsive; fever, if present in the hospital, disappears in twenty-four to seventy-two hours; there is a gain in weight and an improvement in the color. A striking example was that of A.S., a boy 4 months old, who had been in the hospital for eight weeks because of diarrhea. The diarrhea ceased soon after entry but the child continued a downhill course despite all therapeutic efforts. At 4 months of age he weighed less than at birth and his condition was critical. His appearance was that of a pale, wrinkled old man. His breathing was so weak and superficial that it seemed as though he might stop breathing at any moment. When seen twenty-four hours after he had been at home he was cooing and smiling. Though no change had been made in his diet he started to gain promptly and by the end of the first year his weight was well within the normal range. He appeared to be in every way a normal child.

ETIOLOGY OF HOSPITALISM

The failure of babies to thrive in hospitals, referred to as "hospitalism," has been a matter of concern and speculation to the physician since babies were first confined in institutions. For a long time the condition was considered to be due to poor nutrition and deaths were usually attributed to malnutrition or marasmus. However, when application of the newer knowledge of nutrition failed to solve the problem of hospitalism, interest shifted to infection as the cause of the difficulty and obscure deaths in hospitals were generally listed as due to nasopharyngitis and its complications. To guard against cross-infections isolation methods were intensified. The wards for infants were partitioned off into separate little cubicles for each baby, and nurses and physicians were expected to scrub their hands and to wear gowns and masks before handling the babies. Parents were rigidly excluded except for one or two visiting hours each week. Elaborate and expensive boxes were devised, mechanically controlled, in which the babies could be cared for almost untouched by human hands. Manipulation of the babies was discouraged since handling increases the opportunity for bacterial exchange.

For many years thoughtful pediatricians have suspected that the basis for hospitalism was in some vague way related to the infant's psyche. Parrot,⁶ who was associated with several foundling institutions in France, concluded that hospitalism was due to lack of adequate stimulation. Czerny,⁷ felt that monotony and staring at blank walls and ceilings were important factors. Kaupe⁸ emphasized the role of the mothers who could not be replaced by the most self-sacrificing nurses. The psychic and physical influence of the mother, he stated, was a very important weapon against hospitalism. A similar viewpoint was expressed by Pfaundler⁹ who observed that when the mother or some sympathetic person took over the care of the child, severe damage did not take place. Even when many infants were crowded together without special attention to asepsis, that is, under unfavorable environmental conditions, if they were taken care of by their mothers (as was the case in certain foundling institutes in Austria and France), then hospitalism did not play nearly so large a part. Birk¹⁰ held that individual care, which represents a sort of psychic contact between child and nurse, is essential for some infants, and Feer¹¹ believed that

lack of psychic stimulation exercises a harmful effect on the vegetative functions.

Brennemann,¹² recognizing the effect of absence of mothering, had a rule in his hospital that every baby should be picked up, carried around, amused and "mothered" several times a day. An illuminating experience is related by Dr. Fritz Talbot¹³ of Boston. During a visit to the Children's Clinic in Düsseldorf some forty years ago Talbot noticed a very fat old lady wandering about the ward with a very measly baby on her hip. He asked Schlossmann, the Director, who she was and he was told that, whenever they had a baby for whom they had done everything medically and were unsuccessful, they turned the baby over to old Anna and told her to take charge. Old Anna was always successful.

Great credit is due to Dr. Henry Dwight Chapin¹ of New York who was responsible for introducing into America the system of boarding out babies in homes instead of leaving them in institutions. He was keenly aware of the need of babies for individual care and affection.

Some objective evidence of the deleterious effects of institutions on the infant's psyche was presented by Durfee and Wolf in 1933.¹⁴ Using Buehler's tests, they compared the developmental quotients (D.Q.) of infants in various institutions and correlated their findings with the amount of maternal care which the infants received. They found that the groups of infants who had the advantage of maternal care were superior to those who did not, despite the fact that several of the institutions which restricted maternal attention were better equipped and staffed than the others. The observations of Durfee and Wolf have been confirmed and extended by the carefully controlled studies of Spitz.¹⁵

PATHOGENESIS

The way in which emotional deprivation registers its effects on the child is largely speculative but certain rationalizations seem justifiable. According to Rapaport,¹⁶ the emotional process may be initiated in two ways. It may be evoked by an incoming percept from the outside or it may originate from within as, for example, when one gets excited by a novel idea, planning a trip, an anxiety. The stimulus, whether external or internal, initiates an unconscious process which mobilizes unconscious instinctual energies. The discharge process has two components, one which is physiologic and behavioral, the "emotional expression"; the other which is psychologic, the "emotion felt." These may occur simultaneously or they may succeed one another or either may occur alone.

Since young babies obviously lack the mental power to initiate emotion-producing situations, they are entirely dependent on their sensations in this respect. For the same reason the component "emotion felt" is a minor element in the emotional process as compared with "emotional expression." The physiologic and behavioral responses of the young babies to emotion-producing stimuli are not unlike those observed at later ages. Looked at from the very reason-

able viewpoint presented by Rapaport, the question as to whether the emotional responses of the newborn infant can be designated as "fear," "rage," etc., loses much of its point and the same is true for discussions regarding the ability of newborn infants to feel pleasure.¹⁷ In a certain sense young infants may be expected to show purer emotional responses than later on since the pathways for instinctual behavior at this early age are probably wide open and not modified or blocked by cultural conflicts.

The senses—sight, hearing and equilibrium, taste, smell, the skin senses, the muscle senses, the internal sensations—are all functionally active at or shortly after birth.¹⁸ For vision to be meaningful a certain amount of experience is necessary. Moreover, looking is an active process requiring a degree of motor control of the eye and head muscles which is attained only after several months. It is not until 4 weeks of age that the baby has progressed to the point where he will regard a dangling ring.¹⁹ Only later, at 2 or 3 months of age does he begin to respond to a smiling face. This is not true, nearly to the same extent, of the other sensations. The newborn infant shows discriminating behavior toward sounds. He is disagreeably affected by a loud, abrupt noise and he seems pleased by a cooing voice. Sucking seems to give pleasure. Most important to the young baby appear to be the skin sensations and the kinesthetic sense. Babies are readily soothed by patting and by warmth and they cry in response to painful stimuli and to cold. The quieting effect of keeping babies outdoors may well be due, in part, to the movement of air on the skin. That the kinesthetic sense is meaningful is indicated by the soothing effect of rocking and the disagreeable effect of abrupt change in position.

Infants kept in hospitals are, as a rule, manipulated as little as possible. There are two reasons for this: inadequacy of personnel and the fear of transmitting infections. In general the more carefully run hospitals observe stricter "isolation technique" than do others. As a result the infants receive a minimum of sensory stimulation which is their only channel for initiating emotional response. It would appear that the physiologic components of the emotional process are essential for the physical well-being of the young infant and lack of emotional stimulation in early life registers its most profound effects in this sphere.

Later on psychic effects become more apparent. At 8 to 12 weeks of age, as the role of vision enlarges, the infant normally responds to a smile with a smile of his own and a show of animation. This is not the case in infants who have spent some time in an institution. Under these circumstances repeated attempts are necessary before the baby will smile. Presumably psychologic neglect leads to a blunting of the reactivity of the senses to emotion-producing stimuli. Still later, more serious and probably longer enduring psychic effects take place, as the infant begins to distinguish between the individuals in his environment and to establish relationships with them.

It is difficult to explain on the basis of infection alone the prolonged febrile episodes in hospitals and the prompt reduction in fever which takes place when the infants are returned to their homes.⁵ One would hardly expect that the effects of long continued infection would disappear so promptly and constantly.

In this relation an experience with two babies who were admitted to the hospital a number of years ago for custodial care is interesting. During their first two or three months in the hospital these two babies had almost constant temperature elevations which were attributed to upper respiratory infections. Then they both seemed to make an adjustment. They remained free of fever, they gained weight, and they looked healthy and happy. At the time this happy change was attributed to the development of an immunity to ward infections. However, in retrospect, a much better explanation can be found in the fact that these two babies had become the ward favorites and, as such, they were showered with attention and affection by the nurses.

Fever of psychogenic origin has been described in a number of conditions.²⁰ It may be a manifestation of hysteria, it may be induced by hypnosis, it may be associated with excitement and emotional tension in the absence of physical overactivity. Its occurrence in emotionally deprived infants evades explanation at this time.

REMOTE EFFECTS ON PERSONALITY

It is not clear whether permanent damage to the psyche results if babies remain in an institution only during the first three or four months of life, but thereafter the personality distortion which takes place is, apparently, severe and long-lasting. The personality defects which result from prolonged residence in an institution during infancy have been described by Lowrey,²¹ Bender,²² and Goldfarb.²³

According to Bender²² behavior remains infantile, the child using such babyish devices as screaming, kicking, and temper tantrums, in response to frustration. The motor activity is often senseless and poorly patterned. The children are constantly seeking attention. Their relationships lack warmth and they readily shift their attentions from one person to another. They are unable to identify in their relationships to other people.

Language development is defective and later on the defect concerns itself with conceptualization and social concepts. At all levels behavior is impulsive, diffusely unpatterned and unmodified by motivation, discipline, punishment, or insight therapy. There is an inability to enter into and form normal relationships. According to Levy²⁴ lack of normal emotional response is the outstanding personality defect in the emotionally deprived child.

ANIMAL STUDIES

The ill-effects of isolation are by no means limited to the human infant. Throughout the animal world, from the minute microorganisms to the mammals, it seems to be a rule that there is safety in numbers. The deleterious influence of overcrowding has overshadowed appreciation of the protective action of companionship.²⁵

Mice grow poorly when bred in solitude. Chickens raised in solitary confinement develop neurotic behavior. Colon bacilli fail to grow on agar containing gentian violet if singly inoculated on it. Only when thirty or more bacteria are used does steady and regular growth occur under these conditions. Recent

studies have shown a similar protective action of numbers of bacteria in their behavior toward media containing streptomycin.

The devices which groups use to protect themselves are varied. They have been studied by Allee and his co-workers and are summarized in his book on the *Social Life of Animals*.²⁵ Certain flat worms (*Procerodes*) die promptly when a few are placed in fresh water. With larger groups, however, the survival rate is much longer owing to the fact that the few who die give off calcium which exerts a protective action on the group. Goldfish, placed in a silver solution, protect themselves by giving off a substance which precipitates the silver. Grouped Daphnia (water fleas) survive longer than single ones when placed in an alkaline solution by excreting carbon dioxide which neutralizes the alkali. Some animals protect themselves in groups by reducing oxygen requirements. In mice the protective action of numbers seems to reside principally in better maintenance of temperature and the consequent conservation of energy and growth. An additional factor is that mice with injuries about the head can only receive treatment by licking from another individual. Isolated mice with such lesions are quickly cured by their nest mates when they are grouped.

TREATMENT

In 1941, when the thesis that the failure of babies to thrive in hospitals is due to emotional deprivation was presented before the American Pediatric Society,²⁶ babies were no longer dying in large numbers in institutions, as had previously been the case. The reason was that most institutions had closed their doors and were boarding their babies out in private homes instead. The problem of institutional mortality had not been solved; it had been by-passed. The clinical picture of hospitalization, however, was still frequently seen in general hospitals when babies, for one reason or another, were retained in the wards over an extended period; and in the few remaining custodial institutions.

While preparing this report it seemed appropriate to again examine emotionally deprived infants to see whether any clinical features had been overlooked. With this thought in mind I visited, together with Dr. Joseph Di Leo, a large foundling hospital which houses some 250 children, more than one-half of whom are under one year of age. I was unable to find a single baby who showed the clinical features which have come to be associated with emotional deprivation in young infants. The babies showed the motor activity and the ready response to a smile which were so rarely seen in hospitalized babies only a few years ago. The principal reason for this favorable change is the large corps of women volunteers who devote the major part of their time in the hospital to manipulating and playing with the babies.

During the last few years a wholesome change has taken place in the attitude toward the hospital care of infants in the direction of a general relaxation of the rules governing asepsis. In most institutions nurses and interns are encouraged to pick up and carry infants, and many hospitals have volunteers whose principal task it is to play with the babies. This policy has been carried out actively on the Children's Medical Services at Bellevue Hos-

pital for the past twenty years. In addition it has been the custom to assign infants who are doing poorly or who seem unhappy to particular interns for "tender loving care." This device has been well received in most instances and it has often proved as beneficial for the intern as for the baby.

An important measure for preventing hospitalism is the presence of the mother. Where it is necessary to keep a child in the hospital for any length of time as for example, in the case of subdural hematoma, the mother is invited to remain with her baby all day, if possible, and to minister to his wants. This has worked very well. The mother, instead of being a hindrance, relieves the nurses of the care of one patient and she often helps out in the care of other babies.

Contrary to what might have been expected the free manipulation of babies and the presence of parents in the ward has not increased the incidence of infections among the babies. Indeed, there has been a decrease in cross-infections. Since 1930, when an active campaign directed toward satisfying the psychologic needs of babies in the infant's ward at Bellevue Hospital was instituted, the case fatality for infants under one year fell steadily from 30 to 35 per cent to less than 10 per cent in 1938 where it has remained ever since. It is interesting to note that most of the fall in mortality had taken place before the introduction of the chemotherapeutic and antibiotic agents.

Relevant at this point is the experience at the Bassam Clinic, a surgical hospital in New Zealand, where it has been the custom to admit the mothers along with their babies requiring operations, e.g., harelip and cleft palate.²⁷ Each mother and child is provided with a small bed-sitting room where the mother can look after her child exactly as though she were at home. She has the companionship of other mothers in neighboring rooms and she can enjoy the garden where the babies take the air in their carriages. Surgical dressings are done aseptically, generally under light anesthesia to reduce emotional shock. The mother does all the routine work for the baby such as feeding, dressing, changing diapers, thereby saving much time for the nurses. The clinic has been running for five years and during that time there has not been a single case of cross-infection, local or general, and not a single slough or case of dehiscence.

SUMMARY

1. The failure of infants to thrive in institutions is due to emotional deprivation.
2. In young infants emotional reactions arise principally, if not entirely, in response to sensory stimuli. These stimuli set in motion processes that appear to be essential for the child's well-being.
3. To offset the adverse effects of residence in an institution, babies who require hospital care should receive manipulation, attention and affection. Whenever possible, the mother should be at the baby's bedside during the greater part of the day.
4. There is no reason to believe that more handling of the baby and the presence of the mother increase the incidence of infections; indeed, the evidence would indicate the reverse.

REFERENCES

1. Chapin, H. D.: A Plea for Accurate Statistics in Infants' Institutions, Tr. Am. Pediat. Soc. 27: 180, 1915.
2. Hamil, R.: Discussion of paper by Chapin.¹
3. Southworth, T. S.: Discussion of paper by Chapin.¹
4. Knox, J. H. M.: Discussion of paper by Chapin.¹
5. Bakwin, H.: Psychogenic Fever in Infants, Am. J. Dis. Child. 67: 176, 1944.
6. Parrot, M.: Quoted by Czerny.⁷
7. Czerny, A.: Der Arzt als Erzieher des Kindes, ed. 6, Leipzig, 1922, Franz Deuticke, p. 5.
8. Kaupe, W.: Hospitalismus der in Säuglingsheimen untergebrachten Kindern, München med. Wehnschr., No. 8, 1920.
9. Pfaundler, M.: Ueber natürliche und ueber rationelle Säuglingspflege, Vortrag 1909, Sonderabdruck, a.d. Süddeutschen Monatsheften.
10. Birk, W.: Ueber den Einfluss psychischer Vorgänge auf den Ernährungserfolg bei Säuglingen, Monatsschr. f. Kinderheilk. 12: (Orig.), 1, 1919.
11. Feer, E.: Die Ernährungsstörungen im Säuglingsalter und ihre Behandlung, Beihefte z. med. Klinik 1: 25, 1909.
12. Brennemann, J.: The Infant Ward, Am. J. Dis. Child. 43: 577, 1932.
13. Talbot, F.: Transactions of the American Pediatric Society, 1941, discussion of paper by Bakwin,²⁶ Am. J. Dis. Child. 62: 469, 1941.
14. Durfee, H., and Wolf, K.: Anstaltspflege und Entwicklung im ersten Lebensjahr, Ztschr. f. Kinderforsch. 42: 1933.
15. Spitz, R. A.: Hospitalism, an Inquiry Into the Genesis of Psychiatric Conditions in Early Childhood. The Psychoanalytic Study of the Child, A Year Book, New York, 1945, N. Y. International Press.
16. Rapaport, D.: Emotions and Memory, Baltimore, 1942, Williams & Wilkins Co., Chap. 2.
17. Spitz, R.: Emotional Growth in the First Year, Child Study, Spring, 1947.
18. Carmichael, L.: Manual of Child Psychology, New York, 1946, John Wiley & Sons, Inc., pp. 203-226.
19. Gesell, A., and Ilg, F. L.: The Infant and Child in the Culture of Today, New York, 1943, Harper & Brothers, p. 19.
20. Wolf, S., and Wolff, H. G.: Intermittent Fever of Unknown Origin, Arch. Int. Med. 70: 293, 1942.
21. Lowrey, L. G.: Personality Distortion in Early Institutional Care, Am. J. Orthopsychiat. 10: 576, 1940.
22. Bender, L.: There Is No Substitute for Family Life, Child Study, Spring, 1946.
23. Goldfarb, W.: a. Infant Rearing and Problem Behavior, Am. J. Orthopsychiat. 13: 2, 1943.
b. Effects of Early Institutional Care on Adolescent Personality: Rorschach Data, Ibid. 14: 441, 1944.
24. Levy, D. M.: Primary Affect Hunger, Am. J. Psychiat. 94: 643, 1937.
25. Allee, W. C.: The Social Life of Animals, New York, 1938, W. W. Norton & Co., Inc.
26. Bakwin, H.: Loneliness in Infants, Am. J. Dis. Child. 63: 33, 1942.
27. Pickerill, C.: Nursing Mirror, Aug. 16, 1947, Supplement II, quoted by Lancet 2: 588, 1947.

Comments on Current Literature

CHEMOPROPHYLAXIS WITH CHLORAMPHENICOL (CHLOROMYCETIN) IN SCRUB TYPHUS (TSUTSUGAMUSHI DISEASE)

RAPID developments within the past two years concerning the remarkable therapeutic effectiveness of chloromycetin have borne out Smadel's original prediction that this antibiotic would prove of considerable value in the treatment of rickettsial and viral infections. Experimental studies in mice and in embryonated eggs demonstrated the effectiveness of chloromycetin against the rickettsiae of scrub typhus, epidemic and murine typhus, Rocky Mountain spotted fever, rickettsialpox and two strains of psittacosis virus. Administration of the drug to normal volunteers¹ who received maximum single or repeated oral doses showed that the toxicity was minimal. Opportunity for clinical trials in the field presented itself in the treatment of five patients with epidemic typhus.² The same oral doses which had been administered to human volunteers were used, and improvement was observed in all five patients with fall in pulse rate and body temperature and with no noticeable toxic effects. Subsequent opportunity for more extensive therapeutic test³ was afforded in cooperation with the Malaya Institute of Medical Research during an outbreak of scrub typhus at Kuala Lumpur.

Continued reports of the striking effect of chloromycetin on the clinical course of epidemic and murine typhus, scrub typhus, Rocky Mountain spotted fever, of diseases caused by some of the larger viruses, and of some bacterial infections have re-emphasized the importance of this antibiotic substance. The apparent lack of toxicity, the ease of administration by the oral route, the beneficial effect even when administered relatively late in the disease, and the broad coverage of therapeutic effectiveness are outstanding features.

Chloromycetin, obtained originally from strains of *Streptomyces venezuelae* which were isolated from soil and compost,⁴ has been synthesized,⁵ and the synthetic product has been called chloramphenicol. Careful comparative studies⁶ of the effectiveness of the two forms of the drug and preliminary clinical trials with the synthetic form indicated no essential differences. The same low level of toxicity holds true apparently for the synthetic form of chloromycetin.

Following these demonstrations of the effectiveness and minimal toxicity of chloramphenicol, it was suggested by Smadel that this synthetic form of chloromycetin, which is available in larger quantities, might prove of considerable prophylactic value. For example, in rickettsial diseases such as scrub typhus for which thus far vaccines have not been satisfactory, administration of the drug in large doses over relatively long periods might prevent the development of clinical disease in exposed persons. It seemed possible that exposed individuals protected by this means during the critical period of invasion might experience subclinical infection or develop a mild form of the disease, thereby acquiring immunity without the risk of serious rickettsial infection.

For some time Smadel and his co-workers⁷ have been carrying on epidemiologic studies of scrub typhus in hyperendemic areas near Kuala Lumpur,

Malaya. In this connection opportunity for field tests of the prophylactic value of chloramphenicol was afforded.⁸ Human volunteers were exposed in hyperendemic areas. One group of volunteers received chloramphenicol and a corresponding group received a placebo of calcium lactate. Both groups of volunteers were checked daily for evidence of mites of the body and for signs of illness. During the three-week period when the drug was administered, and for eight to ten days after the last dose, chloromyctein suppressed clinical evidence of infection. Following cessation of therapy, however, infection rates in persons "protected" by chloromyctein were essentially the same as those in persons who had received the placebo. With the exception of prolonged incubation period and lower incidence of eschar formation, the disease in members of the prophylactic group was indistinguishable from that in the untreated group.

Laboratory studies in mice carried on simultaneously with the studies in human volunteers showed that viable rickettsiae could be recovered regularly from the tissues of infected mice even when the animals were maintained for three months on daily doses of drug sufficient to prevent the development of clinical signs of the disease. Withdrawal of therapy resulted in infection in these treated mice, and reduction of fatalities was accomplished only by continuing the drug for at least twelve days following clinical onset. The experimental studies in animals indicated likewise that "massive inoculations of rickettsial organisms may break through the protective chemoprophylactic or chemotherapeutic effect of the drug."

The investigations in Malaya are being continued in an effort to understand more completely the process of immunity in this infection, and in the hope of working out an adequate prophylactic regime. Should such a procedure prove practicable and of general application, the prophylactic implications would be of great significance in other rickettsial infections as well as in scrub typhus.

RUSSELL J. BLATTNER.

REFERENCES

1. Ley, Herbert L., Jr., Smadel, Jos. E., and Crocker, Thos. F.: Administration of Chloromyctein to Normal Subjects, *Proc. Soc. Exper. Biol. & Med.* 68: 9, 1948.
2. Smadel, Jos. E., Leon, A. P., Ley, H. L., Jr., and Varela, Gerardo: Chloromyctein in the Treatment of Patients With Typhus Fever, *Proc. Soc. Exper. Biol. & Med.* 68: 12, 1948.
3. Smadel, Jos. E., Woodward, T. E., Ley, H. L., Jr., Philip, C. B., Traub, R., Lewthwaite, R., and Savoor, S. R.: Chloromyctein in the Treatment of Scrub Typhus, *Science* 108: 160, 1948.
4. Erlich, J., Bartz, Q. R., Smith, R. M., Joslyn, D. A., and Burkholder, R. R.: Chloromyctein, a New Antibiotic From Soil Actinomycetes, *Science* 106: 417, 1947.
5. Rebstock, M. C., Crooks, H. M., Jr., Controulis, J., and Bartz, Q. R.: Chloramphenicol (Chloromyctein): IV. Chemical Studies, *J. Am. Chem. Soc.* 71: 2458, 1949.
6. Controulis, J., Rebstock, M. C., and Crooks, H. M., Jr.: *Ibid.*: V. Synthesis, *J. Am. Chem. Soc.* 71: 2463, 1949.
7. Long, Loren M., and Troutman, H. D.: *Ibid.*: VI. A Synthetic Approach, *J. Am. Chem. Soc.* 71: 2469, 1949.
8. Long, Loren M., and Troutman, H. D.: VII. Synthesis Through *p*-Nitroacetophenone, *J. Am. Chem. Soc.* 71: 2473, 1949.
9. Smadel, Jos. E., Jackson, E. B., Ley, H. L., Jr., and Lewthwaite, R.: Comparison of Synthetic and Fermentation Chloramphenicol (Chloromyctein) in Rickettsial and Viral Infections, *Proc. Soc. Exper. Biol. & Med.* 70: 191, 1949.
10. Philip, C. B., Traub, R., and Smadel, Jos. E.: Chloramphenicol (Chloromyctein) in the Chemoprophylaxis of Scrub Typhus (Tsutsugamushi Disease): I. Epidemiological Observations on Hyperendemic Areas of Scrub Typhus in Malaya, *Am. J. Hyg.* 50: 63, 1949.
11. Smadel, Jos. E., Traub, R., Ley, H. L., Jr., Philip, C. B., Woodward, T. E., and Lewthwaite, R.: Chloramphenicol (Chloromyctein) in the Chemoprophylaxis of Scrub Typhus (Tsutsugamushi Disease): II. Results With Human Volunteers Exposed in Hyperendemic Areas of Scrub Typhus, *Am. J. Hyg.* 50: 75, 1949.

News and Notes

The University of Minnesota announces a continuation course in Pediatric Roentgenology on Oct. 31 to Nov. 5, 1949. The course, which will be presented at the Center for Continuation Study, is intended for radiologists and pediatricians. The material to be presented will include the basic medical sciences, clinical medicine, and diagnostic roentgenology, as it pertains to general and special problems in the field of childhood diseases.

Visiting physicians who will participate as members of the faculty for the course will include Dr. John Caffey, Babies Hospital, Columbia University Medical Center; Dr. Edward B. D. Neuhauser, Children's Hospital, Boston; Dr. Edith Potter, University of Chicago; and Dr. Frederic N. Silverman, Children's Hospital, Cincinnati.

A postgraduate course on the Problems of Newborn Infants, Premature and Full Term, sponsored by the University of Colorado School of Medicine and the Colorado State Department of Health, will be given at the University of Colorado Medical Center, Denver, Colo., Nov. 2, 3, 4, and 5, 1949. The guest lecturer is William L. Bradford, M.D., Associate Professor of Pediatrics, University of Rochester School of Medicine, Rochester, N. Y. Inquiries should be directed to Director, Graduate and Postgraduate Medical Education, University of Colorado School of Medicine, Denver, Colo.

Aided by a grant from the National Foundation for Infantile Paralysis, the University of Colorado Medical Center is offering a series of postgraduate courses on poliomyelitis. The courses are open to physicians who are graduates of medical schools approved by the American Medical Association and who reside in states west of the Mississippi. On the calendar for the school year 1949-1950, three one-week courses are scheduled: Nov. 7 to 11, inclusive, 1949; March 13 to 18, inclusive, 1950; May 22 to 27, inclusive, 1950.

Dr. Stuart S. Stevenson, formerly assistant professor of child health at Harvard University, has been appointed research professor of pediatrics at Children's Hospital of Pittsburgh and the University of Pittsburgh School of Medicine effective Sept. 1, 1949.

Dr. Alex J. Steigman is currently serving as full-time Consultant in Clinical Epidemiology for The National Foundation for Infantile Paralysis, Inc. Dr. Steigman's temporary departure from pediatrics will be for the purpose of field work in early diagnosis, management and epidemiologic investigations of poliomyelitis.

Dr. James T. Bosma of Minneapolis, assistant professor of pediatrics at University of Minnesota, has become associated with the medical staff of Elizabeth Kenny Institute in Minneapolis.

Dr. Robert H. Alway has been appointed associate professor of pediatrics at the Stanford University School of Medicine.

Dr. John W. Amesse of Denver died Aug. 21, 1949. Dr. Amesse was one of the pioneer pediatricians in Colorado and was emeritus professor of clinical pediatrics at the University of Colorado. He had always been active in the A. M. A. where he was a member of the house of delegates for many years and vice president in 1943-1944.

Dr. Catherine S. Amatruda of New Haven died Sept. 1, 1949. She had been associated with the Yale Clinic of Child Development for a number of years, and, in collaboration with Dr. Arnold Gesell, was the author of a number of important books on child development.

Book Reviews

Clinical Endocrinology. Lawrence Martin, M.D., and Martin Hynes, M.D., Philadelphia, 1949, The Blakiston Company, 207 pages.

This book has the format of the usual "Synopsis," yet the two Cantabrigians have produced a work more critical and better documented than most books of this type. Each endocrine gland, excepting the pancreas, is discussed briefly from the standpoints of anatomy, physiology, interrelationships with other endocrines, and assay of active principles, with the bulk of the space devoted to the clinical features of dysfunction both diagnostic and therapeutic. References are given at the end of each chapter and a general index is provided. The style is good.

Much of the recent work on the adrenal is missing, and the discussions of the thymus and of childhood obesity seem inadequate. Although the book is well suited to the general practitioner, the availability in current texts of more complete discussions of the endocrine problems of childhood render it less useful to the pediatrician.

FORBES.

Prenatal Care. Publication No. 4 of Children's Bureau, Washington, D. C., 1949, Government Printing Office, 76 pages.

This is a completely rewritten edition of the pamphlet, "Prenatal Care," of which more than 9 million copies have been distributed since the first edition in 1933. The rewritten text takes cognizance of the changes in obstetrical care and our knowledge of pregnancy that have taken place in recent years. Most striking is the change from home to hospital delivery and the gradual disappearance of the midwife. The text is clear and well written for lay reading, and the material has been carefully checked and criticized by competent medical advisers. Throughout, the need for competent medical supervision is stressed during the prenatal period.

A Miniature Textbook of Feeble-mindedness. Leo Kanner, M.D., New York, 1949, Child Care Publications, Child Care Monographs No. 1, 33 pages. Price \$1.25.

This is a stimulating monograph which deserves wide reading by the pediatrician, who, the chances are, first has to face the question and problems of feeble-mindedness in a child. Dr. Kanner discusses the inadequacy of grouping cases on the basis of organic determinants or on the degree of retardation as disclosed by mental tests, or into primary and secondary amentia, and proposes a pragmatic grouping into three divisions: absolute feeble-mindedness, relative feeble-mindedness, and apparent feeble-mindedness or pseudofeeble-mindedness. This classification, in a sense, parallels the tendency of modern psychiatry to get away from the rigid Kraepelin classification of psychoses into specific categories, and to consider the psychotie as an individual, following the influence of Freud and Meyer. The grouping proposed by Kanner would pay less attention to causes and types and look toward the study of feeble-mindedness from the practical standpoint of individual, educational, communal, and medical possibilities. In the study of the individual child Kanner feels that six determinants must be evaluated: genetic, cultural, material, physical, educational, and emotional. On the basis of these six factors, a personal profile of the individual case is obtained. The importance of each determinant is discussed and illustrated from the author's experience. To the reviewer, not a psychiatrist but a pediatrician, who, over the years, has had to face many times the problem of feeble-mindedness in practice and consultation, Dr. Kanner's monograph comes as a practical and common-sense ray of light in what has been a dark, dismal, and pathetic field.

B. S. V.

Editor's Column

RECOMMENDATIONS FOR THE CONTROL OF POLIOMYELITIS

THERE is no disease more upsetting to a community, to health officers, and to practicing physicians than poliomyelitis. This derives from the fact that little exact knowledge exists of how it is contracted and spread, and as a result it is difficult to give satisfactory advice on how to prevent its development in the individual or spread in the community.

As poliomyelitis has become more widespread and common in recent years, with an increasing tendency to assume epidemic proportions, some of the foolish practices that developed in the earlier epidemics have been stopped. We recall how in the epidemic of 1916 in New York some small "upstate" communities stationed police officers on the highways as they entered the village and stopped each automobile. If they carried children an officer was placed on the running board of the car and the driver forced to pass through the town without stopping. Other measures as the closing and opening of schools, theaters, and swimming pools are still matters of acrimonious discussion in many communities, and health officers become the target of panicky citizens on the one hand, and of those whose economic interests are involved on the other.

Last June the National Foundation for Infantile Paralysis called a group of nationally recognized workers in the field of poliomyelitis and in public health to a conference in Ann Arbor to discuss the subject of poliomyelitis control. Recently they have issued a memorandum on "Recommended Practices for the Control of Poliomyelitis."¹ No one will disagree with their findings that there is much "confusion," and that "many existing regulations require practices that are not only ineffective . . . and unwarranted by facts, but also create problems for patients and families." Based on the present limited knowledge of the disease and its epidemiology, the conference has made certain recommendations, among which the following may be singled out as attempting to answer some of the more perplexing questions that are frequently raised:

Control.—There are no preventive measures. Isolation should be for one week from the date of onset, or duration of fever, if longer. Quarantine is of no proved value.

Epidemic Measures.—Isolation of all children with fever should be made pending diagnosis. Postponement of elective nose or throat operations or dental extractions. Avoidance of excessive physical strain. Avoidance of unnecessary travel and visiting.

¹Complete copies of the recommendations of the conference from which these excerpts have been selected may be obtained from the National Foundation for Infantile Paralysis, 120 Broadway, New York 5, N. Y.

Schools.—Public and private schools should not be closed during an outbreak, nor their opening delayed, except schools to which children are transported in busses from widely separated areas may be delayed in opening, and boarding schools should be delayed in opening if in an area where there is an outbreak of poliomyelitis.

Summer Camps may be opened if no outbreak exists in the area, but children should not be admitted from an area where an outbreak exists. When a case develops in a camp new children should not be admitted, but children in the camp should be retained for fourteen days after the last contact with the case.

Places of Recreation and Amusement, as fairs, circuses, theaters, and swimming pools, should not be closed by health officers, but the attendance of children at such places should be discouraged.

While these recommendations reflect the paucity of knowledge regarding the spread and control of poliomyelitis, their formulation by the conference gives the physician and health officer something "authoritative" to fall back on when his opinion is asked, or a decision has to be reached when poliomyelitis appears in the community.

THE ABRAHAM JACOBI MEMORIAL FUND

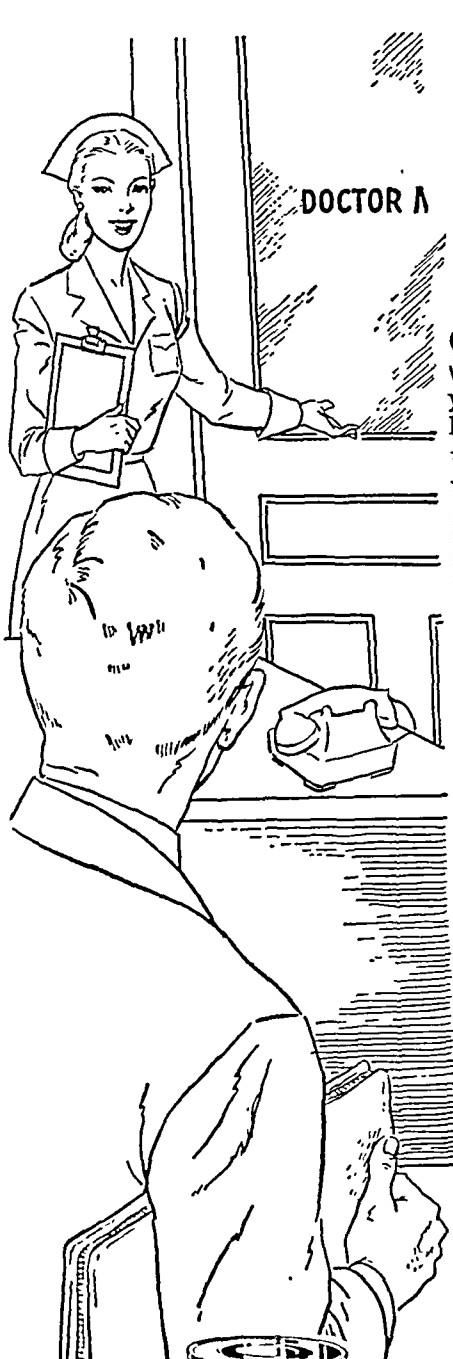
MANY pediatricians are unfamiliar with the Jacobi Memorial Fund which was established over twenty-five years ago by the Section on Pediatrics of the American Medical Association and named in honor of the "Father of American Pediatrics." The fund was the idea of the late Dr. Frank Neff of Kansas City, and its establishment was in large part due to his personal work and efforts. He served as custodian of the fund until his death, when he was succeeded by Dr. Hugh Dwyer. The fund is administered by the executive committee of the section and the custodian. The chief purpose of the fund when it was established was to pay the expenses of distinguished guest speakers at the section meetings. Among the guests in the early years of the fund were Findlay of England, Krasnagorski of Russia, Gorter of Holland, Finklestein of Germany, and Wallgren of Sweden. The trustees were also empowered to use the fund for pediatric purposes of national interest. Thus grants were made to landscape the Abraham Jacobi Memorial Park at Bolton Landing on Lake George, to aid in the expense of publication of the Czerny Festschrift by THE JOURNAL OF PEDIATRICS in 1933, and for a supplement to the American Journal of Diseases of Children on endocrine conditions. The last grant made was a contribution to the expenses of the Fifth International Pediatric Congress in 1948, in fulfillment of a pledge made a number of years earlier for a planned meeting of the Congress which was postponed on account of war.

From 1923 to 1936 many pediatricians made an annual contribution to the fund, and those contributing five dollars or more received bound copies of the Transactions of the Section until the section publications were discontinued by the American Medical Association. For some reason or other the section officers in recent years have made little use of the fund which now amounts to around five thousand dollars, although no solicitations have been made and no contributions received since 1936.

According to the minutes of the meeting of the section in Atlantic City last June, the suggestion was made that the balance remaining in the fund be turned over to a library in Chicago for the support of a pediatric division. The section unanimously voted down the suggestion. This action was correct as this disposition is not in keeping with the purposes of the contributions made by pediatricians throughout the entire country. On the other hand, it was good that attention was brought to the fund remaining idle in a bank for a number of years. If the section officers feel, as they seemingly have in recent years, that guest speakers are no longer desirable, the fund might well be gradually disposed of in grants for pediatric matters of national interest. If this is not feasible and it is found best to terminate the fund completely, we have one suggestion for consideration by the trustees. Abraham Jacobi, in whose memory the fund is named, many years ago gave from his own money to start a Jacobi Library Fund at the New York Academy of Medicine. The Academy was undoubtedly his closest professional interest, and for many years he was most active as president and trustee. The turning over of the Jacobi Fund of the section to the fund he himself started would be a solution satisfactory, we are sure, to all past contributors. However, we still feel there are a number of worthwhile things of national pediatric interest that might be aided by grants in the coming years, and it is best, as the section voted in June, not to make a final disposition of the fund at present.

COOPERATION IN RESEARCH

AN example of the value of interdepartmental research was the award of the "Silver Medal" at the scientific exhibit of the recent A.M.A. session at Atlantic City to a group from the Washington University Medical School for their exhibit on "Angiography in Congenital Heart Disease." The recipients were Drs. Moore and Scott of the department of roentgenology, Dr. Burford of the surgical staff, and Dr. Carson of the pediatric staff. The first publications of this interdepartmental group appeared in the November and December issues of THE JOURNAL OF PEDIATRICS of last year. Modern medicine has become so complex that not only has teamwork become necessary in practice, but, so far as clinical medicine is concerned, in research. Such interdepartmental teamwork, of which this is a striking example, is taking place in many of our medical schools and shows what can be accomplished by cooperation.



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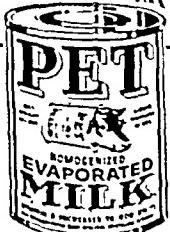
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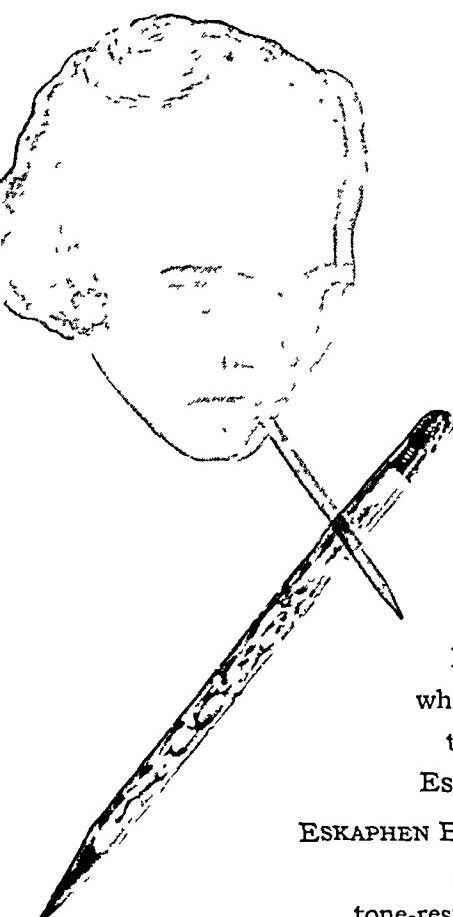
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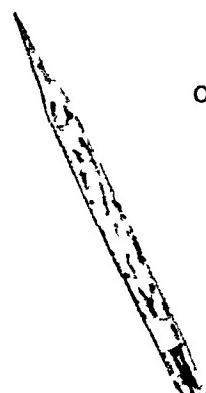
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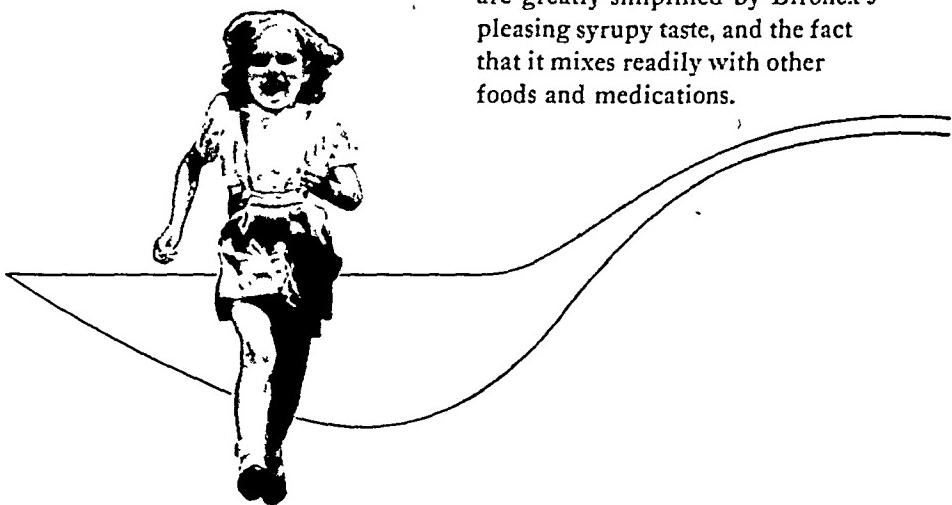
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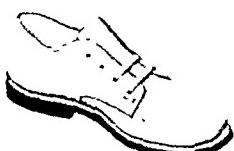


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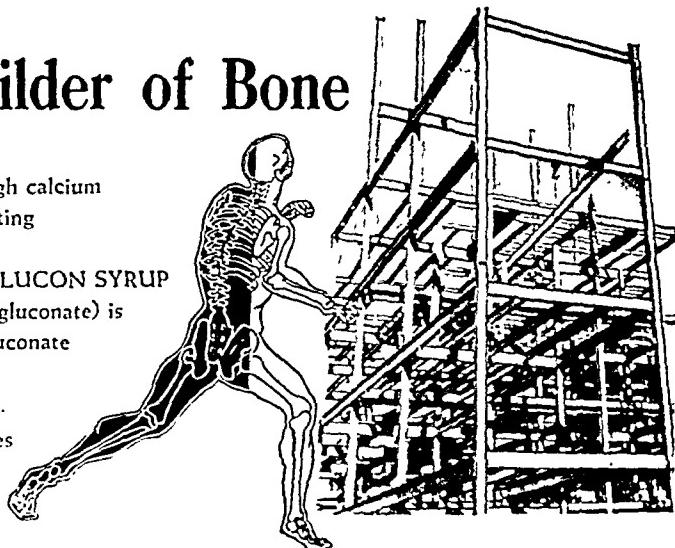
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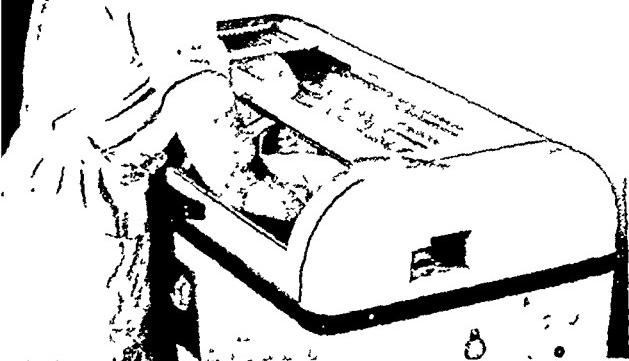
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1. Brown, P. W. Med Clin N Am 33: 957-963, 1949
2. Bockus, H. L. Gastroenterology Philadelphia, W. B. Saunders Co., 1944, Vol. 2, p. 527

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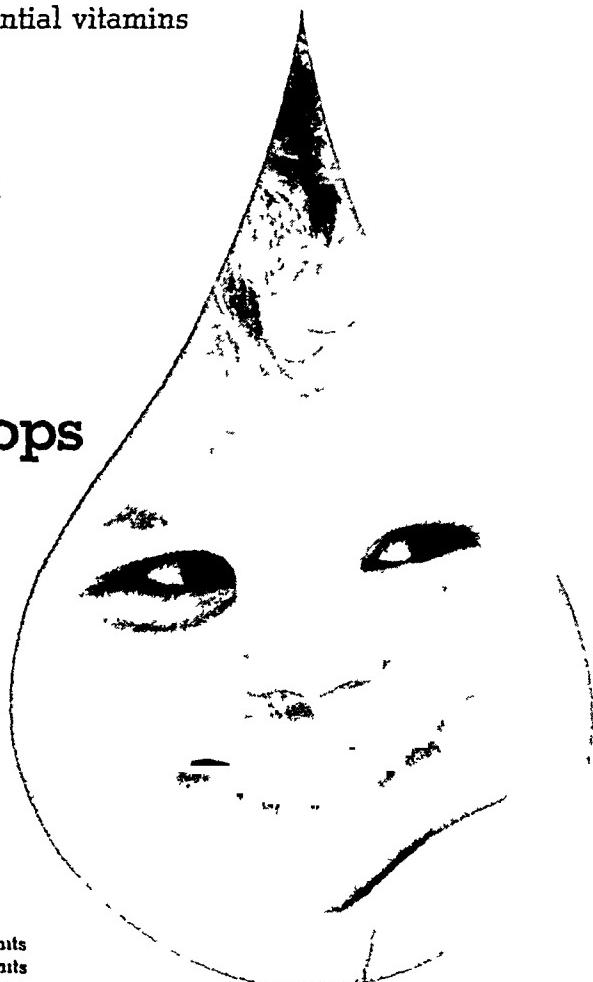
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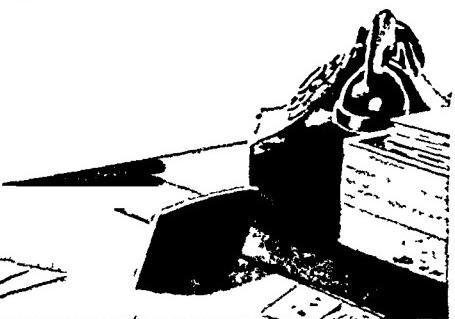
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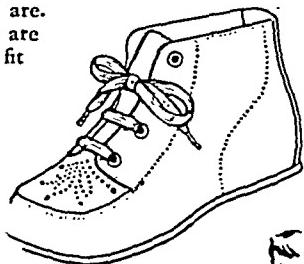


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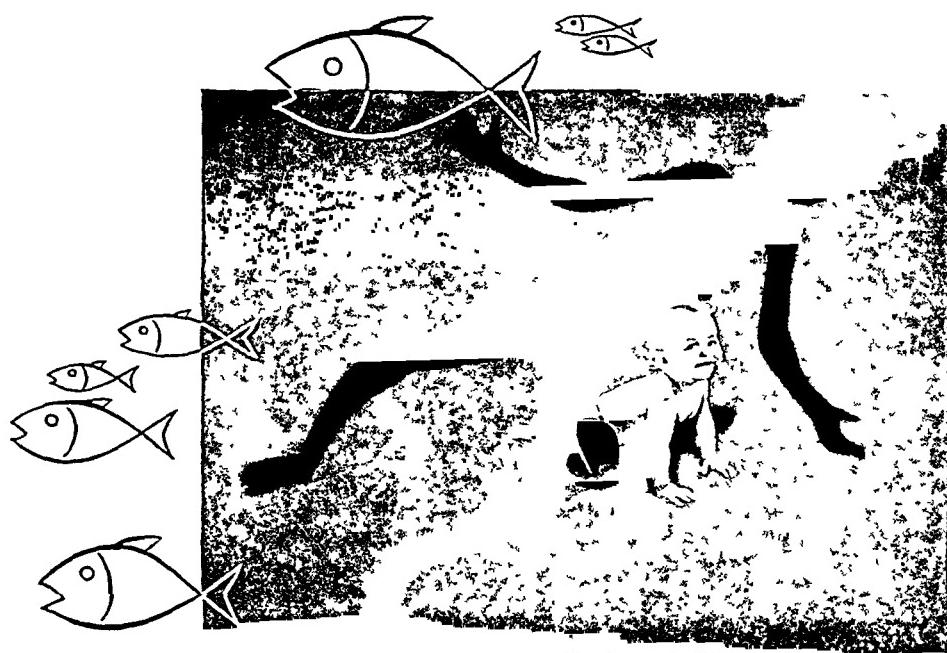
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1. Holder, H. G., and MacKay, E. M.: Mil. Surg. 90:509-518 (May) 1942.
2. Holder, H. G., and MacKay, E. M.: Surgery 13:677-682 (May) 1943.



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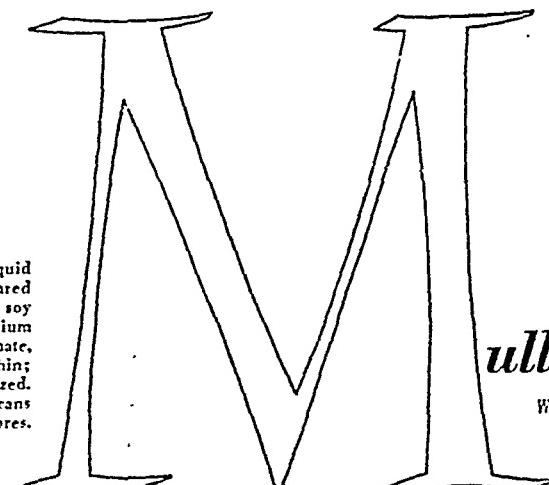
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